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HAEMORRHAGIC DISEASE OF THE NEWBORN

BY

ELIZABETH B. S. SCOBBIE, M.B., Ch.B., D.C.H.

(From the Department of Paediatrics, Glasgow University, the Royal Hospital for Sick Children, Glasgow, and the Royal Maternity Hospital, Glasgow)

There is a wide difference of opinion regarding the criteria necessary for the diagnosis of haemorrhagic disease of the newborn. Formerly, the essential feature seems to have been bleeding from the alimentary tract, hence the synonym ' melaena neonatorum.' More recently a wider view has been taken and many authorities do not consider that haemorrhage into the alimentary tract is necessary for diagnosis, but regard all cases of spontaneous haemorrhage from any organ or tissue, internal or external, in the absence of trauma, infection or any definite disease, as examples of the condition.

Salomonsen (1939), however, claims that the bleeding is seldom spontaneous and is almost always of traumatic origin. Capon (1932), on the other hand, excludes cases which show haemorrhage into internal organs on the ground that such haemorrhage usually results from trauma ; and both von Reuss (1921) and Capon (1932) consider that all cases in which haemorrhage occurs for the first time after the seventh day of life are caused by infection and hence exclude them. Others (Rodda, 1920; Salomonsen, 1939) consider that the basic factor is prolongation of the bleeding time or of the clotting time, or a combination of both, but Schloss and Commiskey (1911), Clifford (1935) and others have drawn attention to the fact that delay in the clotting time of the blood is not a constant feature. Recently, it has been claimed (Hellman et al., 1939; Quick and Grossman 1940; MacPherson, 1941; Salomonsen, 1939) that the primary factor is a deficiency of prothrombin which in turn is due to a deficiency of vitamin K. On the other hand the recent work of Sanford et al. (1942) throws doubt on their conclusions. Snelling (1940), Mengert (1940), Kove and Siegel (1940) consider there are at least two etiological factors, one of which is always hypoprothrombinaemia and Mengert (1940) suggests that the additional factors may be birth trauma, anoxaemia and other causes of bleeding.

Snedeker (1941) draws attention to the increased incidence of asphyxia in his series of cases of haemorrhagic disease of the newborn, as compared with the incidence in other newborn infants; in this connexion there is an interesting account by Cruickshank (1923) of asphyxial haemorrhages occurring in several foetuses whose mothers had died from concealed accidental haemorrhage before the onset of labour. He found petechial and capillary oozings in various situations, and in some instances gross haemorrhage into the viscera. Clifford (1941) described the autopsy findings in eleven infants delivered by Caesarian section before the onset of labour, in cases of placenta praevia. Intra-partum asphyxia from retro-placental haemorrhage was the cause of death in every case, and haemorrhage, along with other evidence of asphyxia, was present in all. He claims that the extreme degree of oxygen deficiency which is present in asphyxia has a direct effect on the blood vessels; it causes congestion, dilatation, escape of plasma and haemorrhage. The smaller blood vessels apparently become fragile and two types of haemorrhage may result: (1) petechial

which is usually widespread, and (2) extensive bleeding in the lungs, liver, heart, alimentary tract and brain. As a result of detailed examination of these cases Clifford (1941) says that ' much of the gastro-intestinal, pulmonary, and liver haemorrhage may be of this origin, and that in the complete absence of trauma, asphyxia may be responsible for varying degrees of haemorrhage into the cerebro-spinal fluid, into the ventricles and into the brain substance itself.'

These findings suggest that asphyxia may be a cause of haemorrhage in the newborn, but they do not afford an explanation for the bleeding in the large majority of cases of haemorrhagic disease.

Haemorrhage in the newborn infant owns many causes. Some of these, such as gross trauma and severe infection, are generally recognized not to be responsible for true haemorrhagic disease, but there are other conditions which are thought by some to play a contributory part in the etiology. The most important of these is minor trauma, insufficient in itself to lead to profuse haemorrhage, but which, when associated with some blood abnormality, is capable of producing gross haemorrhage. For example, in haemophilia bleeding will only occur when trauma supervenes. This raises the difficult question whether or not infants who have low concentrations of plasma prothrombin, and who have incurred mild trauma followed by profuse bleeding, should be classified as cases of true haemorrhagic disease. Snedeker (1941), while questioning the justification for so doing, includes cases in which this haemorrhagic tendency was revealed by such minor trauma as that caused by circumcision or by operation for tongue tie. Some authorities hold that infants with gross intracranial haemorrhage, in the absence of a history of trauma or asphyxia, should be considered as cases of haemorrhagic disease; particularly is this the case when the onset of symptoms is delayed till three or four days after birth.

The problem of classification also arises in cases where there is minor localized trauma but widespread haemorrhages. In such cases Clifford's (1935) recommendation has been adopted. He says that if in addition to local haemorrhage of traumatic origin (in the central nervous system, liver, adrenals) the infant develops spontaneous internal or external haemorrhage in areas not directly related to the injury, the case should be classified as haemorrhagic disease of the newborn. Only one case of this nature is included in the present paper (p. 177). Likewise he recommends that cerebral haemorrhage, occurring in the absence of a history of trauma, and associated with multiple haemorrhages in other areas, should be included.

Difficulty in diagnosis also arises when infection is associated with haemorrhage. It is generally agreed that septicaemia frequently causes widespread haemorrhage, and pneumonia and enteritis may be haemorrhagic in type, giving rise to considerable haemorrhage into the lung or the bowel, and in some cases to bleeding elsewhere. Such cases are clearly not examples of haemorrhagic disease. On the other hand it is questionable whether or not cases with mild and localized infections but with widespread haemorrhage should be excluded.

Lastly, there are certain conditions in which haemorrhage occurs, but which are certainly not examples of haemorrhagic disease. In a considerable pro-

portion of cases of icterus gravis haemorrhage occurs and the picture very closely resembles haemorrhagic disease of the newborn. In a consecutive series of forty-three cases of icterus gravis admitted to the Royal Hospital for Sick Children, Glasgow, haemorrhage occurred in nineteen. When blood has been ingested during labour or from a bleeding nipple, it may be vomited or passed in the stool, and haemorrhagic disease may be suspected. Bleeding from the vagina occurs a few days after birth in about 5 per cent. of normal female infants. This is a physiological phenomenon and has no relation to true haemorrhagic disease.

After excluding the cases of haemorrhage discussed above, there remains a group which appears to be a clinical entity and to which the name of haemorrhagic disease of the newborn has been given. So in the present paper only those cases have been included which conform to the following definition—' spontaneous internal or external haemorrhage in the newborn infant in the absence of trauma, infection or other definite disease ' (Clifford).

Present investigation

One hundred and sixty-seven cases of haemorrhage in the newborn infant (excluding frank intracranial haemorrhage) were admitted to the medical wards of the Royal Hospital for Sick Children from January, 1931, to February, 1942, and the study of their records forms the basis of this report; eighteen have been examined personally. From the total twenty-one have been excluded for the following reasons:—

Fourteen because of infection.

Two cases of haemorrhagic enteritis.
Two cases with pneumonia.
Two cases of septicaemia.
Six cases with umbilical sepsis.
Two cases with septic infection of the skin.

Four because of profuse haemorrhage following minor degrees of trauma. In one of these asphyxia was also a factor.

Three because of vaginal haemorrhage, but with no haemorrhage elsewhere.

In three of the infants excluded because of sepsis of the umbilical cord, the infection was so slight in extent that it was probably incidental, and in another excluded because of septicaemia, it is possible that the infection was superimposed on the haemorrhagic condition. He was a premature infant weighing 2·23 kgm. in whom melaena had been present from the second day. He was transferred to hospital on the eighth day because slight melaena persisted and because he began to vomit all his feeds. On admission to hospital the haemoglobin was 20 per cent. Eighty c.c. of blood were transfused at once, and on the ninth day there was no further bleeding, but the child continued to vomit. On the tenth day fever developed and a submaxillary swelling was seen. The infant died on the twelfth day and the autopsy findings were multiple abscesses in the lungs, scanty abscesses in the kidneys, septic spleen, a submaxillary abscess and petechiae in the small intestine. One case has been included which clinically had true haemorrhagic disease, and in which post-mortem examination revealed, in addition to gross haemorrhage into the bowel, a tentorial tear with subdural haemorrhage. There was a history of difficult instrumental delivery, which would explain the subdural haemorrhage but not the severe bleeding from the stomach and bowel. The haemoglobin fell to 30 per cent. and the red cells to 976,000 per c.mm. An unsuccessful attempt to transfuse the child

was made and death occurred a few hours later. There were no signs of cerebral haemorrhage during life.

After excluding these twenty-one cases the following is an account of the remaining one hundred and forty-six infants who fell strictly within the bounds of the definition of the disease given above.

Age at onset. Haemorrhage began in the first three days of life in one hundred and twenty-eight cases (89 per cent.) and of these it began on the second day in sixty-four cases (44 per cent.). In table 1 is shown the age at onset in the cases of true haemorrhagic disease and in the cases of haemorrhage associated with infection. From this it will be seen that there is a tendency for the haemorrhage to have a later onset in the cases with infection than in those of true haemorrhagic disease, though four of the latter did not show any signs of bleeding until the eighth, tenth and twenty-first days of life in two others.

Two cases in which there was no evidence of haemorrhage clinically, but which showed haemorrhages at autopsy are not included in this table, as the age at onset is not known.

Sex incidence. There was a preponderance of females in this series, the figures being as follows: sixty-one males, eighty-three females, two unstated. That is 57 per cent. of cases occurred in female infants. Most other authors have found that the sex incidence was equal or that there was a slight preponderance of male infants.

Seasonal incidence. In the present series the disease was more prevalent in the first six months of the year than in the second. Ninety-four cases occurred between the months of January and June and fifty between July and December. McCollum (1928) reports a maximal incidence in January with a decrease in the number of cases from April to September. Salomonsen (1939) found that the disease was more prevalent in the winter and spring months (December to June) and draws attention to a similar seasonal incidence in the physiological prolongation of the clotting time in newborn infants. The significance of this seasonal variation and its possible relation to dietary deficiencies, or to infections of the mother during pregnancy, is not understood. There appears to be little difference between the diets of mothers of healthy infants and those of mothers whose infants develop haemorrhagic disease (Salomonsen, 1939; Kove and Siegel, 1940). In this series no details of the maternal diet during pregnancy are available. The mortality rate appears to be independent of seasonal influence.

Place in family. Thirty per cent. of cases occurred in first-born infants, but 25 per cent. occurred in those who occupied the fifth to the fifteenth place in the family. It would appear, therefore, that the place in the family does not influence the incidence of this disease. Other workers (Clark, 1933; Snedeker, 1941; Salomonsen, 1939) have shown an increased incidence in first-born infants.

Influence of abnormal pregnancy, labour or delivery. Details of the pregnancy, labour and delivery are in many cases scanty, and probably often inaccurate, as the history in all these cases was obtained from the father, a relative or a friend. Twelve per cent. of the mothers were delivered by forceps, 6 per cent. suffered from hypertensive toxaemia of pregnancy, and there was a history of prolonged labour in 5 per cent. Antepartum haemorrhage occurred in one case and in nine other cases there was a history of asphyxia at birth. Two of the mothers had twin pregnancies and in both cases one twin only was affected.

Site of bleeding. The commonest source of haemorrhage is from the alimentary tract. One hundred and thirty-five cases out of one hundred and forty-six had either haematemesis or melaena or both. One hundred and eight cases had bleeding from the alimentary tract alone, and six other cases came into this category during life, but at the autopsy showed evidence of

TABLE 1.—AGE OF ONSET OF HAEMORRHAGIC DISEASE AND OF HAEMORRHAGE ASSOCIATED WITH INFECTION

AGE IN DAYS		1	2	3	4	5	6	7	8	9	10	11	12	13	14	21
Haemorrhagic disease	No.	34	64	30	7	3	1	1	2	0	1	0	0	0	0	1
	Per cent.	24	44	21	5·8	2	0·7	0·7	1·4	0	0·7	0	0	0	0	0·7
Haemorrhage with infection	No.	0	4	2	1	2	0	0	1	1	0	2	0	0	1	0
	Per cent.	0	29	14	7	14	0	0	7	7	0	14	0	0	7	0

TABLE 2.—SITE OF HAEMORRHAGE—VARIOUS AUTHORS (CLIFFORD) AND PRESENT SERIES

		INTERNAL AND EXTERNAL BLEEDING								EXTERNAL BLEEDING			
	TISSUE OR ORGAN	SCHLOSS AND COM-MISKEY	CLIF-FORD	BEVE-RIDGE	TOWNS-END	CLARK	DEMBO	JAVERT	SCOBBIE	CAPON	FALLS	CLIF-FORD	SCOBBIE
Percentage of spontaneous haemorrhages reported in various organs and tissues	Central nervous system	—	20	16	10	12	71	7	7	—	—	—	—
	Lungs and pleura	—	23	24	4	—	—	4	9	—	—	—	—
	Skin	30	36	44	42	28	—	20	6	—	—	30	7
	Scalp	—	10	8	4	4	—	—	1	—	—	—	—
	Peritoneal cavity	—	7	8	2	—	—	—	1	—	—	—	—
	Pericardial cavity	—	14	8	—	—	—	—	1	—	—	—	—
	Thymus	—	5	4	2	—	—	4	—	—	—	—	—
	Kidney	10	17	4	—	6	—	6	3	2	—	2	—
	Adrenal	10	20	—	—	—	—	3	1	—	—	—	—
	Liver	10	9	—	—	—	—	1	—	—	—	—	—
	Umbilicus	30	10	28	36	21	2	10	7	+	5	7	6
	Gastro-intestinal tract	60	82	100	82	62	27	64	93	92	100	94	97
	Vagina	—	12	—	—	—	—	8	1	3	—	10	—
	Nose	—	—	—	—	—	—	—	2	—	—	—	2
Total number of cases		10	69	24	18	50	55	72	146	61	14	40	123
Percentage given I.M. or S.C. blood		100	4	58	0	88	35	72	78	50	0	0	84
Percentage given I.V. blood		0	84	8	0	4	13	70	35	13	100	95	38
Percentage given vitamin K analogue		0	0	0	0	0	0	0	16	0	0	0	15
Mortality per cent.		30	33	33	33	38	53	16	16	8	0	0	8

S.C.=subcutaneous I.M.=intramuscular I.V.=intravenous

internal haemorrhage in addition. The bleeding varied in amount from small quantities of altered blood to large amounts of bright red blood in the vomitus or passed per rectum. In most other cases bleeding occurred from more than one site. Table 2 is a table constructed by Clifford (1935) with the addition of the findings observed in the present series. It gives the site of haemorrhage observed by Clifford himself and other workers. It will be seen that there is a marked correspondence between Javert's (1938) figures and those reported in this paper, but the incidence of internal haemorrhages is not as great, either in Javert's (1938) or in the present series, as that reported by other authors. Internal haemorrhage occurred in 42 per cent. of Clifford's (1935) cases as compared with 16 per cent. in the present series. It is possible that this difference is due in part to the fact that practically every infant in the present series was born at home, and not in a maternity hospital where complicated labour, instrumental delivery and asphyxia occur more frequently. Further, in eight of the fatal cases in the present series (33 per cent.), no post-mortem examination was made and it is probable that had permission for autopsy been granted in every case, the incidence of internal haemorrhage would have been somewhat higher, although still lower than that found by Clifford (1935), Townsend (1894), Beveridge (1928) and Clark (1933).

Anaemia. Red blood cell counts, or in the absence of marked jaundice, estimations of haemoglobin at frequent intervals are of great value in determining whether haemorrhage is continuing or has ceased, and in judging the effect of treatment. A sudden fall in the haemoglobin percentage may occur in a very short space of time and transfusion at this stage may be life-saving. The following four examples illustrate this.

Case 1 Hb 90 per cent. on admission, fell to 60 per cent. in 3 hours.
Case 2 Hb 74 per cent. on admission, fell to 43 per cent. in 6 hours.
Case 3 Hb 74 per cent. on admission, fell to 43 per cent. in 6 hours.
Case 4 Hb 78 per cent. on admission, fell to 40 per cent. in 7 hours.

The patient's general condition must be taken into account along with the degree of anaemia as depicted by examination of the capillary blood. The haemoglobin percentage and the red cell count drops as the blood volume is restored following haemorrhage, and the interpretation of these figures is therefore modified by the rapidity of this reaction. The figures quoted suggest that restoration of blood volume may occur rapidly, but in one premature infant whose alimentary tract at autopsy was found to be full of blood, and who must have suffered severe blood loss, the haemoglobin shortly before death was 120 per cent. This patient suffered from internal haemorrhage in addition to haemorrhage into the lumen of the bowel and was very collapsed. There is no doubt that a certain number of deaths is caused by exsanguination. In 19 per cent. of the fatal cases examined post mortem no other cause of death was found.

Bleeding time. The bleeding time was determined in eleven cases. In two severe cases it was ten-and-a-half and five-and-a-half minutes respectively, and in the remaining nine cases it fell within normal limits. It should be remembered that prolongation of the bleeding time may occur in healthy newborn infants and in other conditions than haemorrhagic disease. For example, one case of haemorrhage associated with a severe furunculosis had a bleeding time of nine minutes.

Prothrombin content of the blood. Observations on the prothrombin content of the plasma have been made in fifteen definite cases of haemorrhagic disease of the newborn, and in three cases of haemorrhage associated with infection. Reid's (1941) modification of Quick's method for determining prothrombin was used in every case. A few micro-prothrombin tests were also performed,

but details of these are not included as the results were found to be unreliable. The determination of the prothrombin content of the plasma by Quick's method is dependent on the clotting time of recalcified plasma in the presence of an excess of thromboplastin. The clotting time estimated in this way is called the prothrombin time, and is found to be prolonged in cases with deficient prothrombin. It is not, however, a direct estimation of concentration of prothrombin, but serves as a measure of two factors concerned in coagulation, the prothrombin content of the plasma and its rate of conversion into thrombin. At each estimation the prothrombin time of normal plasma is first determined, and that of the patient's plasma is expressed as a percentage of the normal. This is known as the prothrombin index (Illingworth, 1939).

$$\text{Prothrombin index} = \frac{\text{Normal prothrombin time}}{\text{Patient's prothrombin time}} \times 100$$

In the present series the prothrombin indices on admission to hospital and before treatment was commenced, have been charted in fig. 1, and the cases

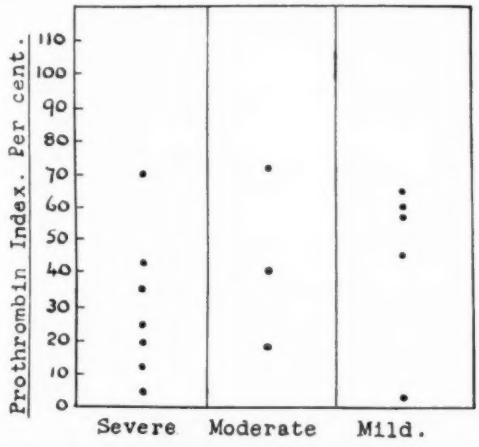

FIG. 1.—Prothrombin index in haemorrhagic disease.

have been grouped into three categories, severe, moderate and mild, depending on the extent of bleeding as judged by the haemoglobin percentage. Infants with haemoglobin over 100 per cent. were classified as mild, those with haemoglobin between 80 and 100 per cent. as moderate and those with haemoglobin less than 80 per cent. as severe. Seven cases fell into the severe, three into the moderate and five into the mild category. The onset of haemorrhage in these cases occurred on the first day in four cases, the second day in seven cases, the third day in four cases. For purposes of comparison fig. 2 shows the prothrombin indices of seventy-five healthy newborn infants on the first three days of life, twenty-five for each day. These infants were chosen from the healthy babies born in the Royal Maternity Hospital, Glasgow. From the figure it is seen that six cases (24 per cent.) on the first day, three cases (12 per cent.) on the second day and two cases (8 per cent.) on the third day have prothrombin indices less than 50 per cent., but in none of these was there any evidence of haemorrhage. While ten of the fifteen cases of haemorrhagic disease had prothrombin indices below 50 per cent., five cases, one severe, one moderately severe and three mild, had indices of 70 per cent., 73 per cent., 65 per cent., 60 per cent. and 59 per cent. respectively. The prothrombin indices in the three cases excluded because of infection were 26, 12 and 62 per cent.

Morbid anatomy. Twenty-four deaths occurred in the series, giving a mortality rate of 16·4 per cent. Sixteen of the twenty-four cases were examined

post mortem. Haemorrhage into the bowel was found in twelve cases, into the lungs and pleura in eleven, into the brain and meninges in four, into the peritoneal cavity in two and from the umbilicus in two. Haemorrhage was also noted once into each of the following organs, the kidney, suprarenal, pericardium, nose, vagina and ear. In only one case was there any evidence of ulceration of the stomach or bowel. In this case small erosions were found in the gastric mucosa. Haemorrhage into the bowel was the only positive finding in 19 per cent. of the cases which were examined post mortem.

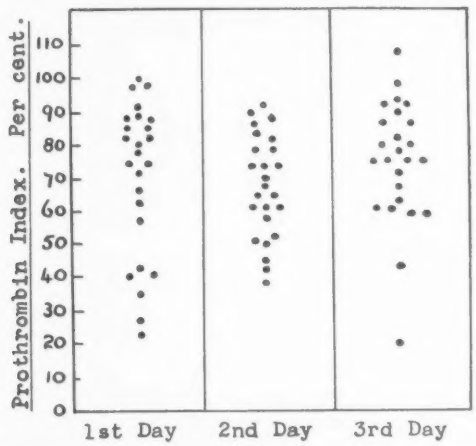

FIG. 2.—Prothrombin index in normal newborn infants.

Treatment. A great variety of remedies has been employed in the treatment of haemorrhagic disease, among others, perchloride of iron, ergotin, tannin, adrenaline and gelatin, but it is probable that none of them is of any real therapeutic value. About thirty years ago Schloss and Commiskey (1911) advocated intramuscular or subcutaneous injection of blood, and till recently this form of treatment, fortified in severe cases with blood transfusion, has supplanted the older methods. Recently, however, doubt has been thrown on the efficacy of blood injection, and with increased knowledge of the etiology of the disease, vitamin K has become the popular remedy. In a critical review of the subject, Clifford (1935) questions the value of all therapeutic agents. From a study of this review and of the reports of other workers, it is extremely difficult to make a true evaluation of the various methods advocated. The chief difficulty arises in the fact that there is great difference of opinion regarding the definition of the disease. Another difficulty arising out of this is the wide range of figures quoted for the mortality rate in untreated cases (35 to 84 per cent.), whilst the fact that transfusion, though not necessarily a specific remedy, is certainly a life-saving measure in exsanguinated infants, adds to the confusion.

The recent work on the rôle of vitamin K and prothrombin in haemorrhagic states has led to the assumption that deficiency of the latter is the cause of haemorrhagic disease of the newborn. Evidence in favour of this view is not conclusive, for prothrombin may be very deficient in infants who show no signs of haemorrhage, and conversely haemorrhage may occurs in infants with a relatively high plasma prothrombin (fig. 1 and 2). If, on the other hand, low prothrombin is the primary cause of the haemorrhage, then there can be little doubt that the administration of vitamin K is the most effective method of raising it to the normal level. In fig. 3 are shown the results of giving (a) subcutaneous blood and (b) a vitamin K analogue to normal newborn infants. From this it will be seen that the administration of vitamin K promptly raised the prothrombin index to between 85 and 115 per cent., whereas the subcutane-

ous injection of blood had little effect. This confirms the work of Sanford and Leslie (1938) and of Lawson (1941) that subcutaneous injections of blood do not raise the plasma prothrombin. For obvious reasons it has been impossible to ascertain the effect of transfusion on the concentration of plasma prothrombin in normal infants, but in table 3, which gives the prothrombin index before and after treatment in nine cases of haemorrhagic disease, it will be seen that in four (no. 3, 4, 5 and 6) there was a definite rise in its level after transfusion. From this table it will also be seen that of two cases given subcutaneous blood (no. 1 and 2) one showed a definite rise twenty hours after the injection while no significant change occurred in the other. Of four cases (no. 7, 8, 9 and 10) treated with vitamin K analogue only, all showed a definite rise in the prothrombin index, but there may be a delay in its action as in two of the cases

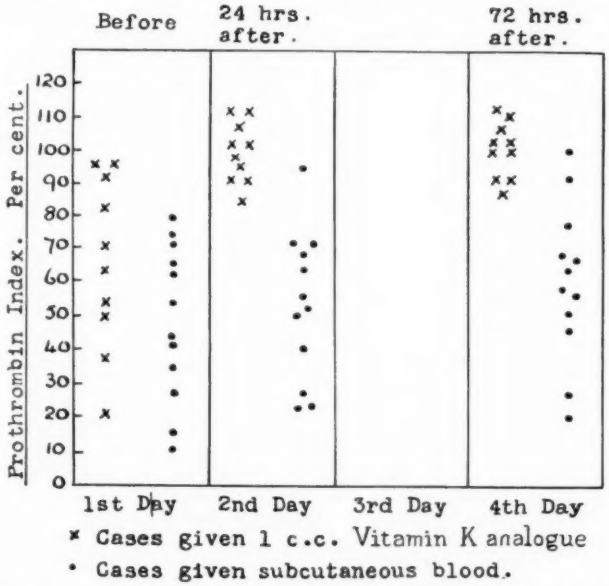

FIG. 3.—Changes in the prothrombin index after giving subcutaneous blood or vitamin K to normal newborn infants.

the rise in the index did not occur till between sixteen and twenty-four hours after its administration.

In the present investigation three methods of treatment have been employed: (1) subcutaneous or intramuscular injections of blood; (2) intravenous blood; (3) vitamin K. In thirty-seven cases treatment by blood transfusion was combined with the injection of blood subcutaneously or intramuscularly, and in eight cases it was given with vitamin K.

It is difficult to estimate the relative value of different methods of treatment in a disease in which spontaneous recovery is known to occur when blood loss is slight, and so an attempt has been made to classify the cases according to their severity, as judged by the percentage of haemoglobin on admission to hospital or later, if a lower reading was obtained. As blood examinations were not always carried out in the earlier years included in this review, a certain number of cases remain unclassified. Table 4 shows the results of treatment of one hundred and thirty-six infants. Ten of the series of one hundred and forty-six cases have been excluded for the following reasons. Two were dead on admission to hospital, two were moribund, four were cases of internal haemorrhage not diagnosed during life, and two were so mild that treatment was withheld. From this table it will be seen that of the fifty-one cases treated

by blood transfusion three died (5·9 per cent.), while of the seventy given subcutaneous blood alone, twelve died (17·1 per cent.) and of the fifteen given vitamin K alone, one died (6·6 per cent.). Excluding those unclassified, of the fifty cases treated by transfusion forty-four were severe as compared with twenty of the fifty-four classified cases given subcutaneous or intramuscular blood only. Taking this factor into account it would appear that intravenous injection of blood is far superior as a therapeutic measure to subcutaneous or intramuscular injections. Owing to the relatively small number of cases treated with vitamin K it is difficult to draw definite conclusions from the figures given in table 4, but as only three deaths occurred in forty-four severe cases treated by blood transfusion compared with one death in the group of six severe cases treated with vitamin K alone, and as six other severe cases treated by the latter method required blood transfusion in addition, it would seem that blood transfusion is more effective as a therapeutic agent than vitamin K particularly in severe cases. Comparisons of the mortality in cases treated by vitamin K and by subcutaneous or intramuscular injections of blood are again limited in value by the small number of cases in the vitamin K group. Of the fifteen cases treated by the latter method one died, and of the seventy cases given blood injections twelve died, whereas the proportion of severe cases was slightly higher in the vitamin K group. Consideration of these results suggests that blood transfusion is the most efficacious method of treatment, next in order of merit comes vitamin K, and last subcutaneous or intramuscular injection of blood. Against the universal use of blood transfusion is the fact that it is a procedure which requires special technique and skill, while the administration of blood by subcutaneous or intramuscular injection and the intramuscular injection of a vitamin K analogue require no special skill and are devoid of danger.

Discussion

When trauma and infection are excluded, the problem arises as to the cause of the spontaneous haemorrhage characteristic of this disease. It has been stated that prothrombin deficiency, which causes a delay in the clotting time of the blood, is the sole etiological factor (Quick and Grossman, 1940). The prothrombin indices in the cases examined in this series compared with those of healthy control infants of the same age, do not give striking evidence in favour of this claim. One would expect the prothrombin index in every case of haemorrhagic disease to be lower than in physiological hypoprothrombinaemia; and relatively lower in severe than in mild cases. That this does not occur is shown in fig. 1 and 2. These findings confirm earlier statements that prolongation of the clotting time is found in only a proportion of cases of haemorrhagic disease. Moreover, unless prothrombin has some function other than that of blood coagulation, it is difficult to understand why blood, whose clotting power is poor, should cause spontaneous haemorrhage, since the function of blood coagulation is not called into play until the closed system of vessels, in which the blood circulates, is broken. If, however, there should be a break in that system, deficiency of plasma prothrombin will no doubt be the cause of a greater quantity of blood escaping than one would expect from the size of the break. The hypothesis favoured by Snelling (1940), Mengert (1940), Kove and Siegel (1940), that there are other factors besides hypoprothrombinaemia, seems to be the most likely one. The favourable results

TABLE 3.—CHANGES IN THE PROTHROMBIN INDEX AFTER VARIOUS METHODS OF TREATMENT

NO.	DISEASE	TREATMENT	PROTHROMBIN INDEX			
			BEFORE TREATMENT (PER CENT.)	5–60 MIN. AFTER (PER CENT.)	4–8 HR. AFTER (PER CENT.)	16–24 HR. AFTER (PER CENT.)
1	Haem. dis.	30 c.c. S.C. blood	25	—	21	82
2	,, ,,	40 c.c. S.C. blood	44	—	—	56
3	,, ,,	30 c.c. S.C. blood	5·5	—	12	—
		70 c.c. I.V. blood	12	—	88	—
4	,, ,,	90 c.c. I.V. blood	35	—	—	100
5	,, ,,	1 c.c. Vit. K analogue	44	—	42	—
		80 c.c. I.V. blood	42	89	—	—
6	Haemorrhage and infection	1 c.c. Vit. K analogue	26	—	49	—
		100 c.c. I.V. blood	49	89	—	—
7	Haem. dis.	1 c.c. Vit. K analogue	40	—	77	—
8	,, ,,	1 c.c. ,,	∞	—	—	71
9	,, ,,	1 c.c. ,,	59	—	68	100
10	,, ,,	2 c.c. ,,	19	—	39	89
11	Haemorrhage and infection	1 c.c. ,,	12·5	—	42	118

S.C.=subcutaneous I.V.=intravenous

TABLE 4.—MORTALITY RATE WITH DIFFERENT METHODS OF TREATMENT

TREATMENT	NO. OF CASES	MORTALITY PER CENT.	SEVERE			MODERATE		MILD			UNCLASSIFIED		
			CASES	DEATHS		CASES	DEATHS	CASES	DEATHS		CASES	DEATHS	
				NO.	PER CENT.				NO.	PER CENT.		NO.	PER CENT.
S.C. or I.M. blood	70	17·1	20	8	40	21	0	13	3	23	16	1	6·2
S.C.+I.V. blood	37	8·1	33	3	9	3	0	0	0	—	1	0	—
I.V. blood	6	0	5	0	—	1	0	0	0	—	0	0	—
Vit. K+I.V. blood	8	0	6	0	—	2	0	0	0	—	0	—	—
Vitamin K	15	6·6	6	1	16·7	3	0	6	0	—	0	0	—

S.C.=subcutaneous I.M.=intramuscular I.V.=intravenous Vit. K=Vitamin K analogue

obtained by treatment with vitamin K, however, suggest that hypoprothrombinaemia is an important factor in the etiology of the disease. In this connexion it has been shown that hypoprothrombinaemia of the newborn can be prevented by the antenatal administration of vitamin K to the mother (Hellman, Shettles and Eastman, 1940; Snelling, 1940), though it has as yet not been proved that such treatment causes a significant reduction in the incidence of haemorrhagic disease of the newborn.

Summary

1. The definition of haemorrhagic disease of the newborn is discussed.

2. One hundred and forty-six cases admitted to the Royal Hospital for Sick Children, Glasgow, between January, 1931, and February, 1942, are analysed.

3. The rôle of vitamin K and prothrombin deficiency in the etiology of the disease is discussed.

4. The effects of treatment by subcutaneous or intramuscular injections of blood, by blood transfusion, and by vitamin K are compared.

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VITAMIN K REQUIREMENTS OF THE NEWBORN

BY

M. TOOHEY, M.D., M.R.C.P.

It has been shown in the last few years, by numerous investigators (Waddel et al., 1939; Nygaard, 1939; et al.) that there occurs an appreciable drop in the prothrombin levels of newborn infants. In an investigation on a small series of sixty infants these results have been confirmed (Toohey, 1941). The fall in prothrombin usually reaches its maximum between the second and fourth days and the level then rapidly rises to nearly normal by the seventh day. This hypoprothrombinaemia is in the majority of cases without clinical significance, but in a very small percentage, where the fall in prothrombin is extreme, the condition of haemorrhagic disease of the newborn occurs. Treatment with vitamin K rapidly restores the prothrombin level to normal with cure of the disease, except when treatment has been delayed, or the condition is extreme.

It has also been shown that prophylactic administration of vitamin K, either before delivery to the mothers or soon after birth to the infant, prevents the fall in the prothrombin level, or markedly reduces it. In a large number of infants treated prophylactically with vitamin K by numerous investigators (Hellman et al., 1940; Waddel and Lawson, 1940) no case of haemorrhagic disease occurred. It can now be assumed that vitamin K is specific for the prevention and treatment of haemorrhagic disease of the newborn. In the investigation recorded below an attempt has been made to find the required dose of a vitamin K analogue which will prevent any fall in the prothrombin level; also the time of administration giving full effect.

Estimation of prothrombin in infants

Estimation of prothrombin in infants is not the simple procedure it is in adults, where Quick's method is reliable. Repeated venepuncture in infants to obtain plasma is not a practical clinical procedure. Most investigators have used a modified form of Quick's method, with whole blood obtained by heel puncture instead of plasma, as advocated by Bray and Kelley (1940). This has been further adapted to tests carried out at the bedside. Whole blood obtained by heel puncture is mixed with an equal quantity of an active thromboplastin solution, and the time taken for a clot to form is the prothrombin clotting time. This is usually expressed as a percentage by taking a control clotting

time. The disadvantage of these tests is the indefinite end-point with blood as compared with the sharp end-point with plasma.

To avoid this Owen and Toohey (1941) obtained plasma from heel puncture by means of white-cell pipettes containing oxalate, and then carried out Quick's test. This simple method gives fairly accurate results. When numerous estimations are being carried out, however, it has the disadvantage of taking up too much time. To expedite the test and to retain the advantage of a sharp end-point, and hence more accurate clotting time, the following method was used:

Dale and Laidlaw's coagulation tubes are used. These are half-filled with an active thromboplastin solution, either brain extract or viper venom. The infant's warmed heel is pricked and the tube is completely filled with blood by capillary attraction, thus giving equal quantities of thromboplastin solution and blood. The remainder of the test is practically identical with carrying out an ordinary coagulation time by Dale and Laidlaw's method. The filled tube is immediately immersed in water at 100° F. (approximately), the ends being firmly closed by forefinger and thumb. The tube is rotated till the bead inside the tube stops, denoting that clotting has occurred. The time from the filling of the tube with blood to the bead stopping is accurately taken by a stop-watch. This is the prothrombin clotting time. The whole procedure takes less than a minute to perform and can be easily repeated two or three times on each infant. The end-point is sharp and can be accurately timed.

The advantages of the above method are the rapidity with which the test can be done at the bedside, the sharp end-point, and hence precise timing, and lastly, the standard conditions of the test. Using this method some hundreds of repeated estimations on infants have been performed and the variation in each case has been found to be usually not more than one second. Variation of more than one to two seconds in any one case occurred mainly in those infants showing a prolonged clotting time, as also occurs when Quick's original method with plasma is used.

Results of estimations on control infants

A. Using method of Owen and Toohey with plasma.

Estimations on sixty infants were made and have been reported in detail elsewhere (Toohey, 1941). A summary of these results need only be given here:

1. Sixteen infants showed prothrombin clotting times of four to ten seconds above adult controls.
2. Eighteen infants showed prothrombin clotting times of ten to twenty seconds above adult controls.
3. Five infants showed prothrombin clotting times of more than twenty seconds above adult controls.

B. Using the method described above with blood instead of plasma.

Estimations on forty infants were made. At least two estimations during the first week of life were carried out and the estimations repeated two or three

times on each occasion. Table 1 shows in detail the prothrombin clotting times of these infants.

TABLE 1

PROTHROMBIN CLOTTING TIMES IN 40 INFANTS—UNTREATED

NO.	1ST DAY	2ND DAY	3RD DAY	4TH DAY	5TH DAY	6TH DAY	7TH DAY	8TH DAY
1		17	19	15		14		
2		17	15			13		
3		14		15		12½		11
4	12		12½			13		
5			17					
6		14			11	14		
7		17	20			15		
8		15		18				
9		16	17		13			
10		13			13			
11		27	40	38		21½		
12	15	19		13				
13		17	16		17½		16	
14	15		16½		14½		14½	
15	15		24	16½		14		
16	17		18½		17½			
17	14		17		15½	15½		
18	14½		15½		16	13		
19	14		17½		13			
20	13		16½	19½	16½			
21	15		29	30				
22	18	18	22					
23		18½	16½	18½		13		
24		20	18	21½		13		
25		15½	16½		18½		13½	
26		16	16½		14½		11½	
27		23	17		16		12	
28				21	15½		14	
29					25	16	14	11½
30		15	15		13			
31	15	19		14½		13		
32		22	25		15		14½	
33		17½	24	17½		16		
34		16½		15				
35		13¼	14					
36	25		13					
37		16	17					
38		17	17					
39		17½		23				
40	14½	14½						
Average clotting time in secs.	15·5	17·2	18·8	19·5	15·5	14·4	13·7	
No. of estimations ..	14	27	30	14	17	15	8	

The prothrombin clotting times obtained by the same method on adult controls were between ten and eleven seconds; eleven seconds is taken as the control time throughout this investigation. A control estimation was performed on each occasion. From table 1 it will be seen that thirty-three infants gave a prothrombin clotting time of more than four seconds above control time of eleven seconds, and of these twelve gave times longer than ten seconds above

control time. It had previously been found that a 50 per cent. prothrombin concentration raises the actual clotting time by only three to four seconds, whilst a 20 per cent. concentration usually raises the clotting time by about ten seconds. It will be seen that a rise of only a few seconds in the prothrombin clotting time denotes a considerable reduction in the prothrombin percentage. It is only when the prothrombin level is considerably reduced that prolonged clotting times of fifteen seconds or more are found. In view of the lack of correlation between the actual prothrombin clotting times, and the prothrombin percentage concentration present, it is preferable to express results of prothrombin esti-

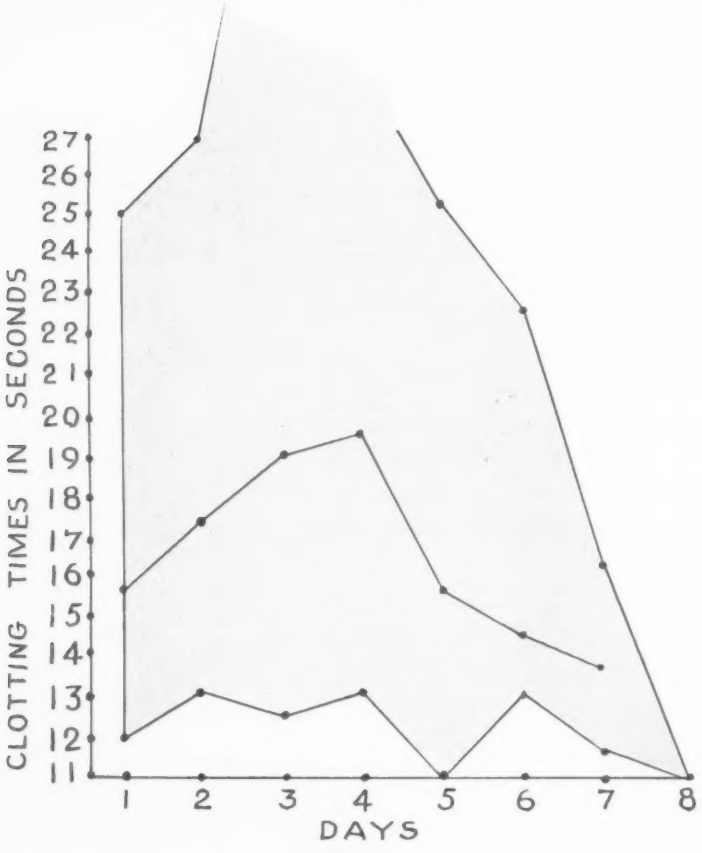

FIG. 1.

mations in actual clotting times and not as percentages. This gives a truer clinical picture when accurate determination of prothrombin is not obtained as in all bedside tests. Fig. 1 shows the limits of variation of the clotting times for each day in these forty infants.

It will be seen from the results of repeated estimations on a hundred infants that a definite hypoprothrombinaemia exists during the first week of life.

Results of administration of vitamin K analogue to mothers and infants

Synthetic vitamin K, 2-methyl-1:4 naphthoquinone (Kapilon), was the preparation used throughout this investigation. The doses given to mothers

and infants were decided on purely empirical grounds. From previous experience it was found that large doses of vitamin K analogue had no harmful effects on infants, so that it was decided to err on the large side. The series was divided into four groups each receiving different doses of vitamin K analogue either to the mother and infant, or infant alone.

Group I. 50 mgm. vitamin K analogue was given to twenty-nine mothers before delivery and 3 mgm. to the infants, six to ten hours after birth. The mothers received the vitamin at least two hours before delivery and usually not longer than sixteen to twenty hours. The average time of administration of the vitamin was approximately six hours before delivery for all groups.

Results of the prothrombin estimations for this group are shown in table 2.

TABLE 2

PROTHROMBIN CLOTTING TIMES IN 29 INFANTS—TREATED

Mother given 50 mgm. vitamin K before delivery
Infant given 3 mgm. vitamin K 6 to 10 hours after birth

NO.	1ST DAY	2ND DAY	3RD DAY	4TH DAY	5TH DAY	6TH DAY	7TH DAY	8TH DAY
1		17½		13½		13		12½
2		15		13		12		
3		13		14		13		13½
4	15		14		14		13½	
5		16			15		14	12½
6		16		14		13½		13
7		12½			13½		13	
8		12½			17	17		13½
9	15	13½		13½		13		
10	16		14		15		15	
11		13		14		14		
12		15		15				12
13		15		15				12½
14		13		16				12
15		14		13½		12½		11
16		15		15		13		
17		14		12½		12		
18	14		12½		12½			
19	13		12½		12½			
20		13		12				11
21	11			12		11		11½
22				13		12		11½
23			16		13		11½	
24			14		13½		12	
25		12		11½		11		
26	17		15½	15				12
27	12½		13½	12				
28	12½		13½				11	
29	11		11					
Average times	13·7	14·1	13·6	13·5	14	12	12·8	12·1
No. of estimations ..	10	17	10	18	9	13	7	13

Eight infants gave prothrombin clotting times of more than four seconds above adult controls of eleven seconds. The longest clotting time for this group was, however, only 6½ seconds above controls. The average time for each day is shown at the end of the table and it will be seen that the longest average time above control time is only three seconds. Fig. 2 shows the variation from shortest to longest clotting times for each day. It will be

readily seen that the limits of variation are considerably reduced when compared to fig. 1, representing the untreated infants.

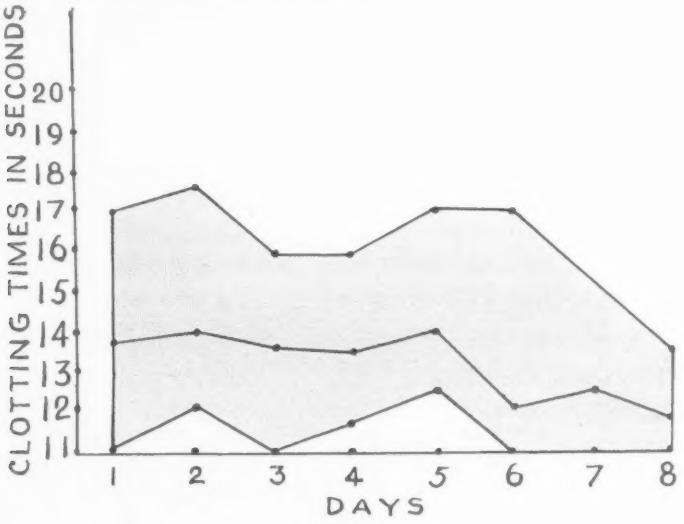

FIG. 2.

Group 2. 20 mgm. vitamin K analogue was given to twenty-four mothers before delivery and 10 mgm. to each infant four to eight hours after birth. Table 3 shows the results of the prothrombin estimations.

TABLE 3

PROTHROMBIN CLOTTING TIMES IN 24 INFANTS—TREATED

Mother given 20 mgm. vitamin K before delivery
Infant given 10 mgm. vitamin K 4 to 8 hours after birth

NO.	1ST DAY	2ND DAY	3RD DAY	4TH DAY	5TH DAY	6TH DAY	7TH DAY	8TH DAY
1	13		13		12			
2		14		13		12		
3	13		13½		13			
4	15		14	13½			12½	
5		14		12		11½		
6		13		12		12½		
7	15	13			12½			
8		13	13½				11	
9		12		12½				11
10	13½	13½	13½				11½	
11	12½	11½				11½		
12	12½	12				11		
13			12	11		11		
14		13	13		12		11	
15		13		11		12		11½
16		13		11		12		11½
17		13		14	12		13	12
18		14	14		12½		13	13
19		12½		11		11		
20		12½		11		11		
21	13		12		11		11	
22	11½		13½	11	11			
23	12		11		11			
24	13		12½	11		12	11	
Average times	13·1	12·9	12·9	11·8	11·8	11·5	11·7	11·8
No. of estimations ..	11	16	12	13	9	11	8	5

No infant gave a prothrombin clotting time of more than four seconds above control time of eleven seconds, the longest time for this group being four seconds above controls. The longest average time for any one day was only two seconds above control time. Fig. 3 shows the limits of variation of clotting

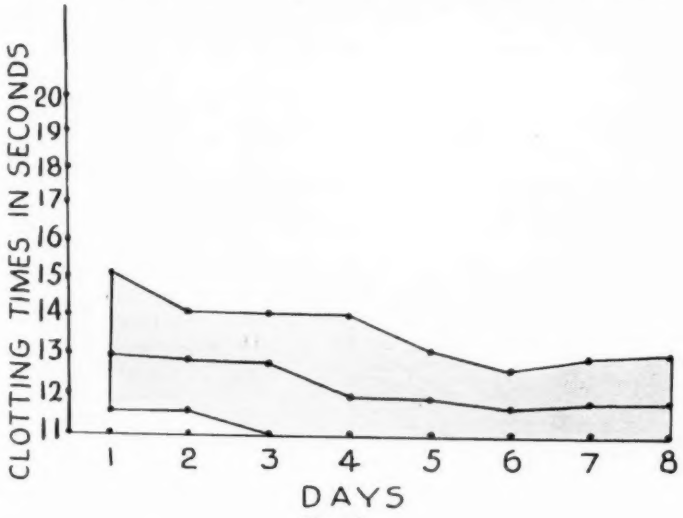

FIG. 3

times for each day. It is at once seen that these are markedly reduced as compared to fig. 1 for untreated group.

Group 3. 20 mgm. of vitamin K analogue was given to seventeen mothers before delivery and 5 mgm. to each infant four to six hours after birth. Table 4 shows the prothrombin clotting times for the group.

TABLE 4

PROTHROMBIN CLOTTING TIMES IN 17 INFANTS—TREATED

Mother given 20 mgm. vitamin K before delivery
Infant given 5 mgm. vitamin K 4 to 6 hours after birth

NO.	1ST DAY	2ND DAY	3RD DAY	4TH DAY	5TH DAY	6TH DAY	7TH DAY	8TH DAY
1	11½		11		11½		10	
2		14	12	11½		12		12
3	13		11		11½		11	
4	12		13	12½		11½		
5	12½		11½			11		
6		13	12			11		11
7	12	12			11½		11½	
8	12½	11		12		11		
9	14		12		12½		11	
10	12½	12		13½		12½		
11			11	11		12		
12	13	13	13		11½		13	
13	13	11		14		14		
14	12½	12½		13		13		
15	11	13	14		13			
16	12	14		14		14		
17	11½			14	14		14	
Average times	12·3	12·5	12	12·7	12·2	12·2	11·7	11·5
Estimations	14	10	10	9	7	10	6	2

The longest prothrombin clotting time was three seconds above control of eleven seconds. The longest average time for any one day was less than two seconds above control. Fig. 4 shows the limits of variation of prothrombin

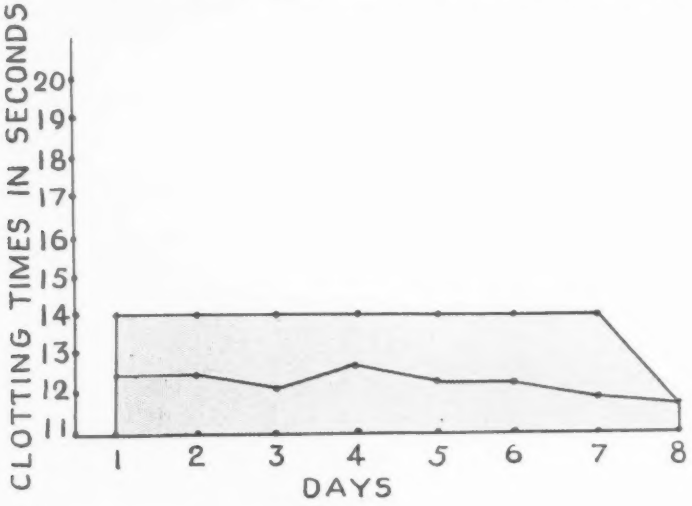

FIG. 4.

clotting times. It will be seen that the results in this group are practically identical with those of group 2.

Group 4. 10 mgm. of vitamin K analogue was given to twenty-eight infants five to eight hours after birth in a single dose. No vitamin was given to the mothers. Table 5 shows the results of the prothrombin estimations.

While twelve infants showed a rise greater than four seconds above control, the longest prothrombin clotting time was only six seconds above control time. The longest average time for any one day was less than four seconds above control time. Fig. 5 shows the limits of variation of clotting times for

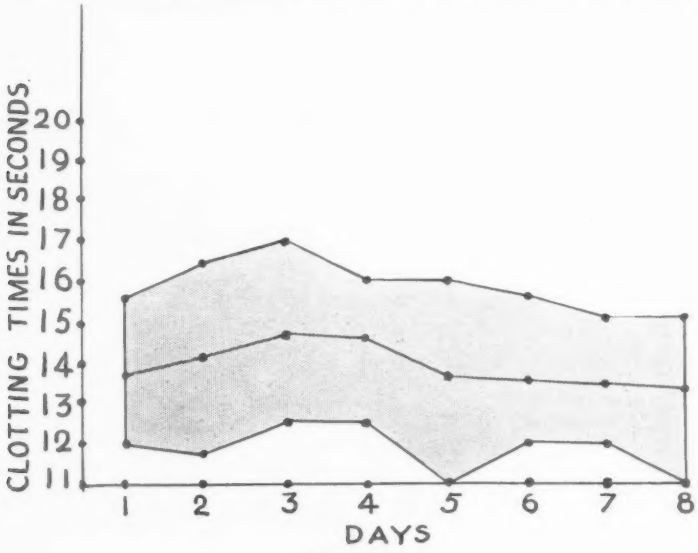

FIG. 5.

this group. It will be seen that while the prothrombin times for this group are considerably lower than the untreated infants, they are definitely longer than those of groups 2 and 3.

TABLE 5

PROTHROMBIN CLOTTING TIMES IN 28 INFANTS—TREATED

Infants given 10 mgm. vitamin K 5 to 8 hours after birth

NO.	1ST DAY	2ND DAY	3RD DAY	4TH DAY	5TH DAY	6TH DAY	7TH DAY	8TH DAY
1		12		16		14		
2		11½		15		13		
3		15		13		14		
4	13		13		11			
5	12		13½		11½			
6		14	13		12		14	
7		16½	16	13½	12			14
8		12½	15		15		15	13
9		14½	15		14			13½
10	13		17	16		15		14
11	15	16½	15	15			14	15
12		13½		15½		13½		
13		16	16	15½		15½		15
14		13	15½		16		13½	
15		14½	14½			12		
16			15	14½		14½		12½
17		15	15		15		12	
18		15	15½		15		13	
19		15		15		14½		14½
20	15½		15½		13		13½	
21		15½	14½		15		14	14½
22	14	13		12½		12		
23		13		14½		12½		12½
24		14		13		13½		
25		13		13½		12½		
26		16	15		15½			
27		16	14½	15				11
28		12	12½					
Average times	13·7	14·2	14·7	14·5	13·7	13·5	13·6	13·4
No. of estimations ..	6	23	19	15	12	13	8	10

Discussion

Prothrombin estimations were carried out on forty infants on at least two occasions during the first week of life. Whole blood obtained by heel puncture drawn into Dale and Laidlaw coagulation tubes, previously half-filled with an active thromboplastin solution, was used for these estimations. Thirty-three infants gave prothrombin clotting times of more than four seconds above adult controls, and of these, twelve infants gave clotting times longer than ten seconds above controls. These times, according to investigations carried out previously, represent approximately a prothrombin concentration of 50 per cent. and 20 per cent. respectively. Two of these infants showed a marked prothrombin deficiency giving clotting times of thirty and forty seconds. None of the infants showed any sign of haemorrhagic tendencies, except that in most infants slight

bruising occurred at the site of the heel puncture; in contrast to this, no infant who had vitamin K analogue showed the slightest sign of haemorrhage around the heel puncture.

In addition to these forty infants, prothrombin estimations on sixty infants, using plasma instead of blood, have previously been reported. A summary of these results shows that thirty-six infants gave prothrombin clotting times of more than four seconds above controls, and of these twenty-three showed clotting times of more than ten seconds above controls. It is therefore evident that a definite hypoprothrombinaemia exists during the first week of life.

Synthetic vitamin K, 2-methyl-1:4 naphthoquinone, was given in varying does to mothers and infants in ninety-eight cases. These were divided into four groups. In group 1, twenty-nine mothers received 50 mgm. vitamin K analogue at least two hours before delivery and the infants 3 mgm. some hours after birth. In group 2, twenty-four mothers received 20 mgm. vitamin K analogue and the infants 10 mgm. In group 3, seventeen mothers received a similar dose of 20 mgm., but the infants received 5 mgm. In group 4, twenty-eight infants received 10 mgm. of vitamin K analogue, the mothers none. In all four groups the administration of the vitamin had a very appreciable effect. The longest prothrombin clotting time in all groups of ninety-eight cases was 6½ seconds above controls; this compares with thirty-five infants out of one hundred showing clotting times of more than ten seconds above controls in the untreated series. The best results were obtained by giving a dose of 20 mgm. of the vitamin to the mothers before delivery and 5 or 10 mgm. to the infant some hours after birth. A single dose of 10 mgm. to the infant alone while not producing quite so good a result, was totally effective in preventing any material drop in the prothrombin level during the first week. The administration of the above doses of 2-methyl-1:4 naphthoquinone to the mothers and infants practically restores the prothrombin concentration to normal adult levels. A smaller dose than 20 mgm. to the mother was not tried in the small series, but it is probable that a reduction to 10 mgm. may be just as effective. The vitamin in all cases was given orally, in tablets to the mothers, and in liquid solution to the infants. No harmful effects were observed even in the largest doses used. No diarrhoea occurred in any of the infants.

There does not seem any need to give vitamin K analogue to mothers during the last days of pregnancy as a prophylactic measure. The vitamin is effective if given during labour and at least two hours before delivery and combined with a small dose to the infant after birth. If the mother has not been given the vitamin, an adequate dose to the infant some hours after birth is sufficient to prevent any material fall in the prothrombin level.

Considerable interest has lately been aroused in the value of vitamin K therapy in lowering the incidence of intracranial haemorrhage in the newborn. Vitamin K is here supposed to act by preventing oozing from damaged capillaries in infants exposed to intracranial trauma, in forceps delivery and difficult labour. There is no doubt that in infants with a severe hypoprothrombinaemia and hence prolonged clotting times, the occurrence of trauma during labour would be likely to result in some degree of intracranial haemorrhage. In these cases

prophylactic treatment with vitamin K would be of benefit. The occurrence of hypoprothrombinaemia sufficiently severe to show haemorrhagic tendencies (such as bleeding from cord stump) is, however, rare. Hence, to hope that the neonatal mortality from intracranial haemorrhage will be materially reduced by prophylactic treatment with vitamin K is optimistic. Some authors have published reports on some hundreds of cases with and without treatment with vitamin K, and showing that the neonatal mortality is considerably lower in the treated group. Before the value of vitamin K in relation to neonatal mortality can be truly assessed, many thousands of cases will have to be carefully analysed, as so many factors enter into neonatal deaths. Huber and Shrader (1941) report two fatal cases of intracranial haemorrhage out of six neonatal deaths in a series, all of whom had vitamin K analogue. As these authors rightly point out, actual clotting is only one of the factors in the control of haemorrhage. The permeability and fragility of the capillaries must also play an important role.

Summary

1. A simple bedside method for the estimation of prothrombin in infants is described.

2. Prothrombin estimations on one hundred infants show that a definite hypoprothrombinaemia occurs during the first week of life. Seven infants showed a fairly severe prothrombin deficiency but in no case was there any haemorrhagic manifestation.

3. 2-methyl-1:4 naphthoquinone in doses of 20 mgm. to the mother before delivery and 5 mgm. to the infant raise the prothrombin level to almost adult control levels. A single dose of 10 mgm. to the infant is entirely effective in preventing any appreciable fall in the prothrombin concentration.

4. It is sufficient to administer vitamin K analogue during labour to be effective, if it is given at least two hours before delivery.

The vitamin K analogue 2-methyl-1:4 naphthoquinone (Kapilon) used in this investigation was kindly supplied by Glaxo Laboratories, Ltd.

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GASTRIC ACIDITY DURING THE FIRST YEAR OF LIFE

BY

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Prior to Cutter's investigations in 1938, the general belief was that there was little or no increase in gastric acidity during the first year of life. Hahn (1914) adopted this view after testing ninety-one specimens taken from thirty-seven infants before and after a milk feed. Hess (1913) and Griswold (1925) agreed, but added that the range of normal was extremely wide. In 1926, Wills and Paterson estimated the total acidity in eight infants after a milk feed; the maximum values for each individual lay between 49 and 70 c.c. N/10 HCl and the investigators were not convinced that age influenced the results. More recently, Klumpp and Neale (1930) using cream to stimulate the gastric secretion showed that there was a possible upward trend in acid concentration during the second six months of life. The results were not conclusive since only sixteen infants under one year were tested and of these only two were from seven to twelve months old. Steimann's (1936) results were also in agreement with those of previous investigators.

Marriott (1923) realized the difficulties of estimating gastric acidity in infancy by test feeds consisting of milk, for he states that not only is the buffer action of milk great, but the buffer constituents varied with the source of milk supply. Moreover, this phenomenon explains the occurrence of large amounts of combined acids with little or no free acid in many of the test-meal specimens obtained in the present investigations. Muller (1928) and Tomotake (1930) avoided the above difficulties by using either barley water or a solution of wheat flour and sugar, which have a feebler buffer action than milk. The latter author was thus able to demonstrate an increase in the total acidity and a fall in the pH of the gastric contents with advancing years, as has been stated by Babbott (1923) and five other authors quoted by him. Their conclusions, however, did not apply to infants under a year old. Babbott (1923) examined the gastric contents of thirty-nine infants one hour after they had taken a feed of dried skimmed milk with these results :—

TABLE I

AGE IN MONTHS	NO. OF BABIES	pH	
		RANGE	AVERAGE
2–3	8	4·6–5·2	4·7
4–6	19	3·5–5·5	4·4
7–9	11	4·0–5·2	4·5
12	1	3·8	3·8

In America, Cutter (1938) noted a rapid increase in gastric acidity during the first year of life (see table 2) and a much slower increase from the end of that period until the fourth year of life when the values almost reached adult standards, i.e. 53 c.c. average free acidity and 67 c.c. total acidity for the children as compared with 86 c.c. and 92·5 c.c. in adults after histamine stimulation (Chang, 1933). To demonstrate this Cutter injected histamine, 0·02 mgm. per kgm. body weight hypodermically into infants starved for three to eight hours in whom the fasting juice had been removed. Four specimens of gastric contents were then taken off at ten minute intervals and analysed for free and total acidity.

TABLE 2
CUTTER'S SERIES

AGE (MONTHS)	MAXIMUM ACIDITY C.C.	
	F.A.	T.A.
6½	27	40
11½	80	105
17	45	156
18	63	74
25	41	53

Present investigation

Cutter's results have been confirmed without the use of histamine. The babies up to one month old were starved for eight hours, the rest obtained food three hours prior to investigation. A number six rubber catheter lubricated with glycerin or liquid paraffin was then passed into the stomach and its contents sucked out into a 10 c.c. syringe. Half an hour and one hour after a test-meal consisting of equal parts of milk and water, and amounting to 60 minims per pound body weight, had been given, a second and third sample of gastric contents were taken. All infants up to a month old, and two-thirds of those three and six months old received breast-milk and water, but older infants during the first year of life had cow's milk and water. The presence or absence of milk was noted, and the quantity of free and total acidity determined in the usual way. One technical difference was that the sodium hydroxide used for the titration was placed in a micro-burette in a dilution N/70.

Results. As stated in a preliminary report upon the behaviour of the gastric acidity during the first week of life (Miller, 1941), free hydrochloric acid was detected in all but twelve per cent. of the fifty healthy breast-fed infants whose gastric contents were examined daily during this period. Usually on the first or second day of life it was consistently greater in the fasting juice than after food. During the latter half of the week even after a meal of milk and water free acid was almost always absent. The total acidity ranged from 5 to 100 c.c. N/10 HCl per 100 c.c. gastric contents, and the highest values were recorded during the first two days of life, almost always in the fasting specimens. For the remaining part of the week the variation in the amounts of total acidity throughout the test-meal was small, and by the seventh day of life it was

remarkable how in almost every case the half-hour and one-hour specimen after a feed contained more acid than in the sample taken while fasting. This transition in the type of secretory response to a meal is represented in chart I.

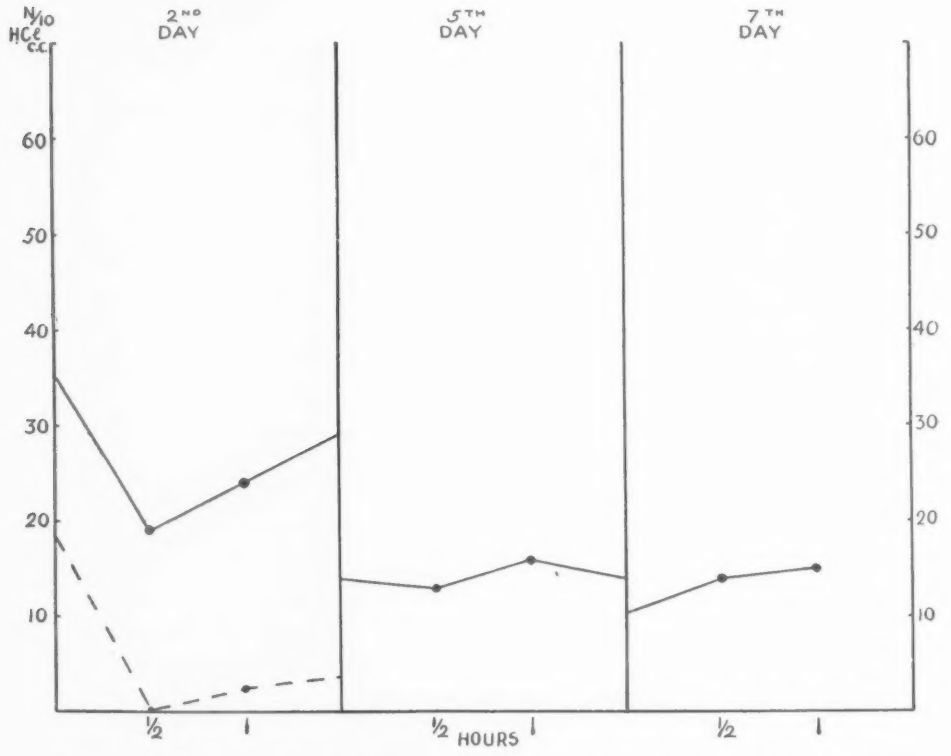

CHART I.—Continuous line indicates average total acidity. Interrupted line indicates average free acidity.

In healthy breast-fed infants two weeks old, the behaviour of the gastric secretion was found to be similar to that at the end of the first week of life. Free acid was only detected once out of sixty test-meals performed at this age. The combined acid generally fluctuated in any given individual less than 10 c.c. and rarely more than 20 c.c. The average figures given in chart II are slightly higher than those for the previous week.

When the infants were three weeks old hydrochloric acid definitely re-appeared ; it was found in three out of twenty-one fasting juices and in half the specimens taken one hour after a meal. The average amount of combined acid was also higher than those for the preceding week (see chart II). After a more detailed study of the results it was found that the maximum acidity followed the giving of food except for four out of twenty-one cases.

A corresponding number of healthy breast-fed babies were tested when they were four weeks old. Free acid was present in the same percentage of specimens as in the last group, while the average figures for total acidity were all elevated (see chart II). It was strange that the values for twenty premature infants of this age were greater :

TABLE 3

		MATURE INFANT C.C.	PREMATURE INFANT C.C.
Fasting juice	F.A.	3	3
	T.A.	23	25
Half hour p.c.	F.A.	0·5	0·5
	T.A.	21	33
One hour p.c.	F.A.	6·5	15
	T.A.	25	31

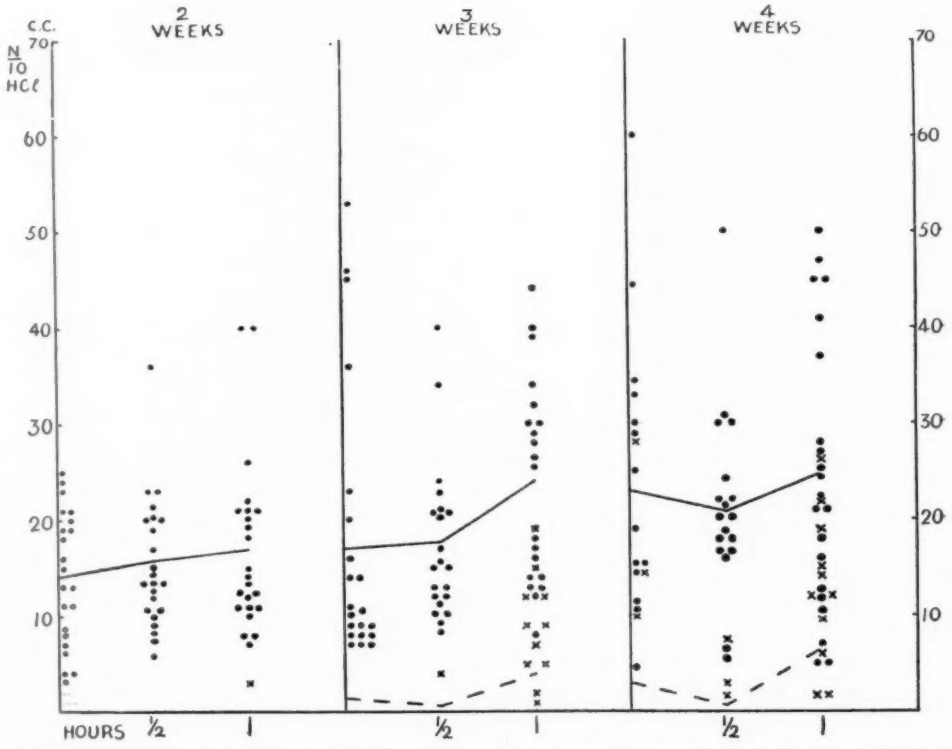

CHART II.—*Dot* indicates individual estimations of total acidity. *Cross* indicates individual estimations of free acidity. Continuous line represents average total acidity. Interrupted line represents average free acidity.

It is difficult to explain this finding on physiological grounds as the infants were all healthy and given breast milk from birth. The premature infants, however, had never been discharged from hospital whereas the mature infants went home with their respective mothers ten days after delivery.

In twenty infants, twelve weeks old, free acid was present in seventy-six per cent. It definitely occurred more frequently after they had been fed, whether the half-hour or hour specimen was examined. The striking change in the behaviour of the total acidity was not only the raised average values but also the growing range between maximum and minimum figures during the test, which amounted to 80 c.c. and 7 c.c. respectively, the average being 34 c.c. (chart III). During the twenty-fourth week and the twelfth month of life

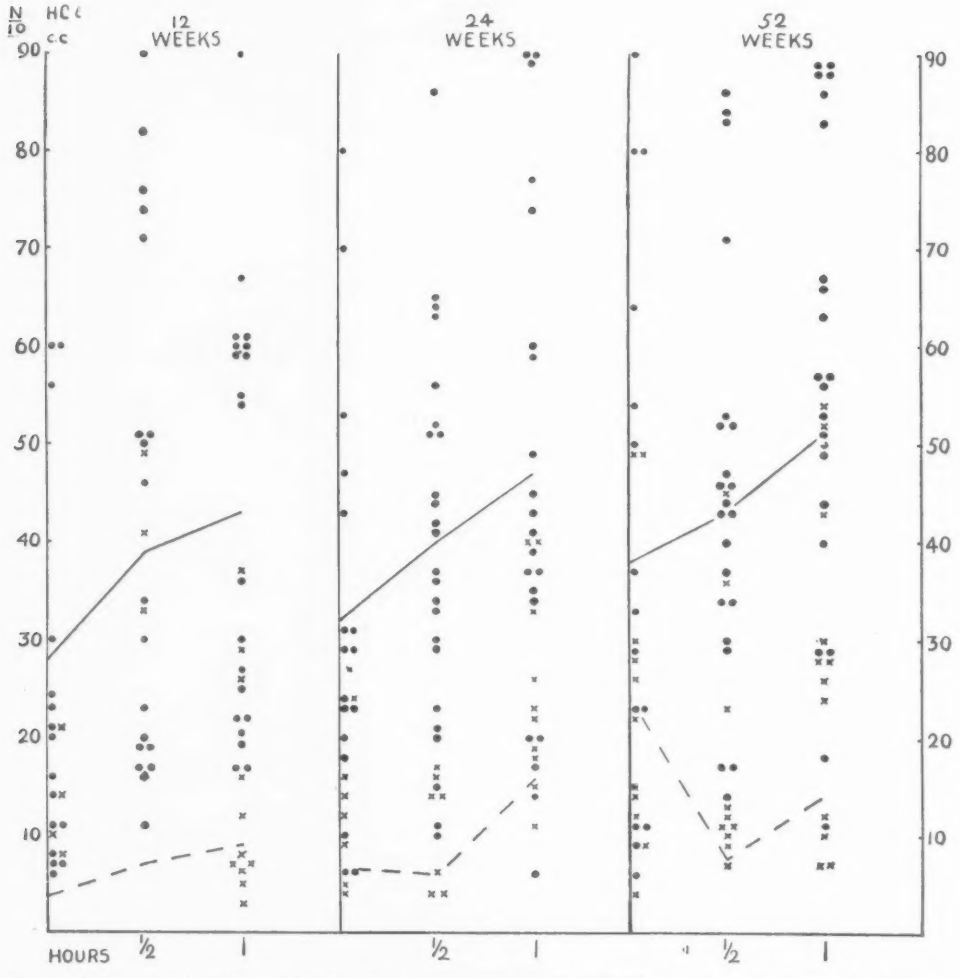

CHART III.—*Dot* indicates individual estimations of total acidity. *Cross* indicates individual estimations of free acidity. Continuous line represents average total acidity. Interrupted line represents average free acidity.

little alteration in gastric secretion was found, apart from the tendency of the concentration of acid to rise. The salient feature was the great range of normal for free and total acidity ; even throughout the tests the fluctuation in degree of total acid was generally great and averaged 28 c.c. and 40 c.c. for each age group. The highest values were recorded in 73 per cent. to 82 per cent. of cases one hour after a feed of milk and water (chart III), and are equivalent to adult figures following a meal of either cow's milk or human milk (Hawk and Bergeim, 1938).

COMPARISON OF FREE AND TOTAL ACIDITY. The difference between these two values is approximately twenty units in an adult. Similar values in some fasting juices were obtained during the first year of life, but in the majority of samples, taken either before or after the test meal, this figure was exceeded.

This is explained by the presence of relatively concentrated and potent buffer substances in the milk and these neutralized the free acid, a fact

vividly demonstrated by examining gastric residue of forty-four infants which contained either milk or gruel three hours after a feed. In all but one of these specimens the values of total acidity were higher than the average for its age group, while the free acid was slightly more, or less, than the average.

TABLE 4

DIFFERENCE BETWEEN FREE AND TOTAL ACIDITY

AGE IN DAYS	FASTING JUICE, C.C.	½ HR. P.C., C.C.	1 HR. P.C., C.C.
1	21	—	—
2	25	37½	28
14	—	—	37
21	47	32	23
28	28	30	31
84	34	36	28
168	26½	35	30½
365	14	36½	38

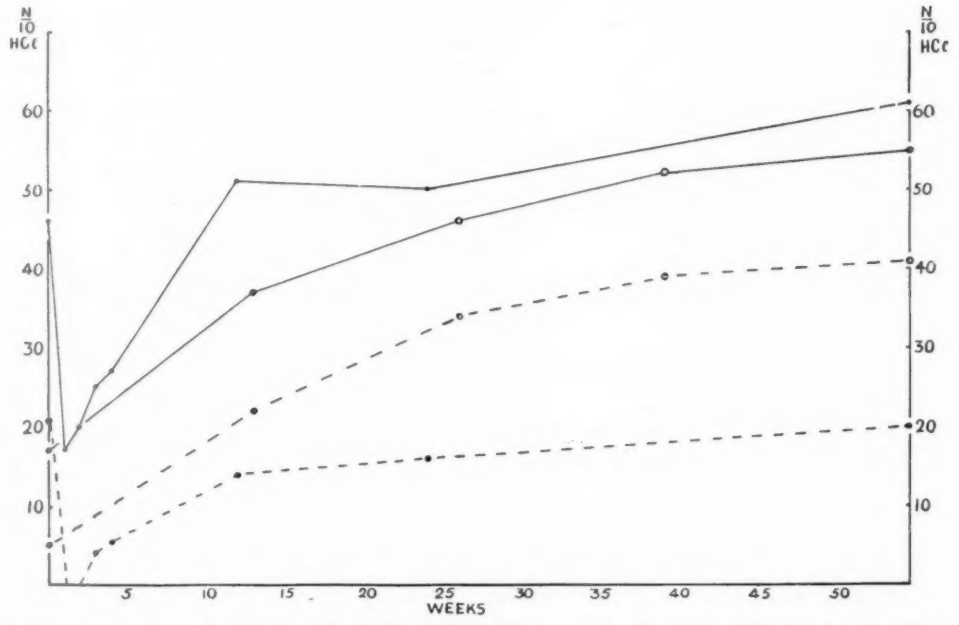

CHART IV.—*Dots* signify values obtained in present series of cases. *Circles* signify values obtained by Cutter (1938). Continuous line represents average total acidity. Interrupted line represents averege free acidity.

Table 5 also shows that at least fifty per cent. infants aged one to twelve months require more than three hours for their stomachs to empty after a milk feed, bread and milk or gruel and milk. Therefore, it is preferable to starve infants for eight hours before performing such a test.

ACHLORHYDRIA. Oliver and Wilkinson (1933), in the most recent and extensive review on achlorhydria in both adults and children, did not believe

TABLE 5

AGE GROUP IN WEEKS	NORMAL FASTING JUICE			CONTAMINATED FASTING JUICE		
	NO. CASES	F.A., C.C.	T.A., C.C.	NO. CASES	F.A., C.C.	T.A., C.C.
3	20	1½	17	3	6	59
4	14	3	23	8	2½	61
12	17	4	28	15	7	86
24	18	5½	32	10	1	86½
52	15	24	38	8	23½	88

any conclusion could be drawn as to the state of affairs in infants owing to the lack of adequate statistics. In the newborn infant, most investigators (Tangl, 1906; Hess, 1913; Pollitzer, 1921; Griswold, 1925; and Faber, 1927) are of the opinion that anacidity is non-existent, a view not shared by Miller (1941) who failed to find free hydrochloric acid in the gastric residue of six out of fifty normal infants who were examined daily for the first ten days of life. Moreover, one of these babies, No. 3874, exhibited achylia gastrica two years later, even after the administration of histamine. This baby, No. 3874, was born on March 30, 1940. His birth weight was 6 lb. 11 oz. He was born spontaneously and normally. The infant grew up to be a strong healthy child and when two years old (March 23, 1942), his gastric content was examined three hours after a meal of bread and milk. The sample contained some bread and its total acidity amounted to 23 c.c. N/10 HCl. per 100 c.c. gastric contents, free acids being absent. The infant was then given histamine 0·2 mgm. hypodermically. Two additional samples were then obtained from the stomach at twenty minute intervals. The last two samples still contained remnants of the bread and milk feed but no further rise in total acidity was recorded, 14 c.c. and 26 c.c. being present. Free hydrochloric acid was still absent. Incidentally it was noticed that cutaneous hyperaemia of head and neck occurred about ten minutes after the histamine injection, thus showing the efficacy of the drug.

The incidence of apparent achylia gastrica following the standard test-meal of milk and water throughout the first year of life is variable; it was recorded in a hundred per cent. of infants two weeks old, forty and thirty-five per cent. when three and four weeks old respectively, and only half the latter figure at three, six and twelve months old. From this time onwards until adolescence there is a small but progressive reduction of achlorhydria with Ewald or modified Ewald test meals (see table 6). The occurrence of true achylia is probably much less, for Cutter (1938) only noted four cases out of ten healthy infants in the neonatal period following an injection of histamine, 0·02 mgm. per kgm. body weight. Thereafter he did not record another case in a series of thirty-five infants in the first year of life. In this last group Lehmann (1935) tested thirty infants, one of which was twelve months old and it exhibited achylia after 0·2 mgm. histamine. No older infant or child has been shown to have this deficiency after histamine administration as judged by investigations upon twenty-one infants aged one to four years (Cutter, 1938) and sixty between six months and twelve years of age (Ogilvie, 1934). Therefore, it may be concluded that the incidence of both anacidity and hypoacidity diminishes rapidly during the first year of life. In older infants or children anacidity is probably exceptional, whereas the incidence of hypochlorhydria shows a slow but definite reduction with age. According to the literature changes of this

nature during the first to twelfth year of life are associated not only with a linear increase in concentration of gastric acidity (Vanzant, 1932; Ogilvie, 1934) but also an increase in volume of the gastric juice (Neale, 1930). These factors are also probably responsible for the changes in gastric acidity during the first year of life.

TABLE 6

AUTHOR	NO. CASES	AGE IN YEARS	PERCENTAGE ACHLORHYDRIA
Klementsohn (1923)	111	1–12	5·3
Dietrich (1931)	14	4–12	7
Wright (1924)	250	6–15	1·6
Copeman (1928)	50	8–16	10·6
Copeman (1929)	66	12–15	10·6
Oliver (1933)	—	20	4

This gastric anomaly has been explained by several theories which include gastritis, neurogenic or constitutional disorders. Of congenital abnormalities, persistence of the infantile glandular state and an inborn deficiency in the functional capacity of the gland are most important in the production of achylia gastrica in infancy and childhood. For example the subnormal structural development of the acid secretory elements in premature infants has been shown to accompany the increase in frequency of achlorhydria.

In addition histological examination of mature infants' stomachs has shown that they may also have a primitive gastric mucosa, of a type usually found in newborn infants weighing three pounds (Scott, 1925; Miller, 1941). Bauer (1921) is also a strong supporter of this theory. The opposing view that achlorhydria is an inborn deficiency in the functional capacity of the gland which has a normal structure is held by Hurst (1923), who noted that pathological changes in the stomach in achylia are so slight and patchy that there can be no question of achylia arising from actual destruction of the secretory cells. This conclusion is supported by the present observation that newborn babies as a rule secrete free hydrochloric acid, sometimes in high concentration, and yet at a week old fail to do so. Furthermore it has also been shown that there is a diminution in the incidence of hypochlorhydria up to the age of twenty.

RELATIONSHIP OF ANACIDITY TO DISEASE. Ill health, malnutrition, allergic disease, as well as certain skin diseases and vomiting, may result in a reduction in gastric acidity. It is questionable whether eczema should be included, for Cutter (1938) found high concentrations of free acid in the stomachs of five infants suffering from this condition after they had received histamine. In the present investigations seven babies, less than twenty-eight weeks old, had localized or generalized eczema and yet no more than a doubtful hypochlorhydria existed (table 7). This suggests that treatment of such cases with lactic acid milk benefits them not by making good the deficient secretion but in a manner comparable to altering the diet of a person suffering from epilepsy or asthma.

Persistent vomiting in infancy, from various causes, results in a more acid

gastric secretion (Wills and Paterson, 1926; Stiemann, 1936), but with pyloric stenosis, (Salmi, 1937), hypochlorhydria tends to develop.

TABLE 7

GASTRIC ACIDITY OF BABIES WITH ECZEMA

AGE (WEEKS)	DURATION OF ECZEMA (WEEKS)	SITE OF LESION	FASTING JUICE C.C.		½ HR. P.C. C.C.		1 HR. P.C. C.C.	
			F.A.	T.A.	F.A.	T.A.	F.A.	T.A.
9	4	General	0	44	0	33	0	27
14	2	Scalp	0	9	0	27	17	43
22	2	Head	0	6	0	30	0	40
10	2	Face and trunk	4	46	0	31	7	30
7	2	Face	0	27	0	21	0	25
31	1	Face	0	6	0	24	2	37
27	14	Head	0	94	6	86	20	70

Additional facts regarding gastric function before and after the development of this disease can be learnt from the three case records :—

BABY NO. 6202, was born on January 18, 1941, weighing 7 lb. 10 oz. He was the first child of a mother who had bilateral pulmonary tuberculosis and was delivered with forceps after 50½ hours labour. The baby's general condition at birth was good and he was fed on cow's milk and water. At two weeks old he was 5 oz. below birth weight and his progress had been normal apart from vomiting twice when twelve days old and once the next day. During the third week of life he never vomited his feeds and was discharged from hospital at the end of that week weighing ¾ oz. more than he did at birth. Two standard test-meals were given to this infant, one when two weeks old and the other when three weeks old. The quantity of the fasting juice did not exceed 0·2 c.c. and contained no milk. One hour after the test-meal there was only a trace of milk curd left in the stomach. The quantity of acid present showed no deviation from the normal.

The baby returned to hospital eleven days later (February 19, 1941) because of vomiting. He had lost 12 oz. owing to pyloric stenosis. On the second, third and fourth day after re-admission to hospital the gastric residue measured 6–20 c.c. and contained milk eight hours after a feed. The total acidity was 23–100 c.c. while on only one occasion free acid, 3 c.c., was present. Ultimately, the infant was treated surgically and the diagnosis confirmed.

	AT 2 WEEKS C.C.		AT 3 WEEKS C.C.	
	F.A.	T.A.	F.A.	T.A.
Fasting juice ..	0	8	0	23
Half hour p.c. ..	0	13	0	17
One hour p.c. ..	0	13	0	12

F.A. indicates free acidity in c.c. N/10 HCL per 100 c.c. gastric contents.
T.A. indicates total acidity in c.c. N/10 HCL per 100 c.c. gastric contents.

BABY NO. 5756. Born on December 29, 1940. Weighed 6 lb. 13 oz. He was the first child of a healthy mother aged thirty-eight who was delivered by

Caesarian section. At first he progressed normally but slowly, his weight being 6 lb. 6 oz. when two weeks old. Two days later vomiting started and persisted to the end of the third week of life when his weight had fallen to 6 lb. ½ oz. and the diagnosis of pyloric stenosis was established. The baby was therefore treated surgically and the diagnosis confirmed. A standard test-meal performed at the age of two weeks, i.e. prior to vomiting, did not suggest gastric stasis as the volume of the fasting juice was only 2 c.c. and contained no milk after fasting for eight hours. There were 6 c.c. combined acid in the fasting specimen and 20 and 13 c.c. in the half hour and one hour specimens respectively. After two days of vomiting the volume of the fasting juice after eight hours of starvation was abnormal; it measured at least 10 c.c. and consisted chiefly of milk. There were 30 c.c. free acid and 63 c.c. of total acidity.

BABY NO. 6893 was a normal female infant weighing 7 lb. 10½ oz. at birth (April 21, 1941) who exhibited pyloric stenosis during the third week of life. When two weeks old she was 7 oz. below birth weight but had not vomited. On the sixteenth day of life vomiting began and the infant's weight fell each day until she only weighed 6 lb. 3 oz. at three weeks old. Three days following the onset of vomiting (May 9, 1941) the infant was given the standard test-meal of milk and water after fasting for eight hours; the fasting juice contained a large amount of milk and its volume was 30 c.c. Specimens removed half and one hour after the test feed were easily obtained and milk was present in both. At no time was free hydrochloric acid found in the stomach contents but the total acidity in each specimen measured 103 c.c., 31 c.c. and 38 c.c. respectively. The infant was operated upon two weeks after the symptoms of the disease appeared and the diagnosis of pyloric stenosis was substantiated.

In pyloric stenosis gastric secretion prior to the onset of symptoms is normal in quantity and acidity, but as soon as vomiting occurs there is gastric stasis, the gastric residue measuring over 4 c.c. and containing milk eight hours after a feed. The free and total acidity is raised in these specimens but later achlorhydria develops. The combined acids, however, remain persistently elevated. Such findings are not pathognomonic of the disease, and have been recorded in severe cases of idiopathic diarrhoea and vomiting.

MOTILITY OF THE STOMACH. According to Davidsohn (1921) and Szasz (1930) the motility of the stomach in childhood varies directly with gastric acidity and muscular tonicity of the gastro-intestinal tract. This may explain the diminishing emptying time of the stomach throughout the first year of life, as illustrated by the following table.

TABLE 8

AGE IN WEEKS	NO. CASES	MILK IN STOMACH 1 HOUR P.C.
1	20	Generally ++
2	23	Trace or +
3	21	Trace or +
4	21	Generally absent
12	20	Absent in 50 per cent. cases
24	21	Absent in 40 per cent. Trace in 43 per cent.
52	22	Absent in 41 per cent. Trace in 14 per cent.

The stomach in infancy almost certainly requires more than one hour to empty (Moritz, 1933) for a normal feed is generally more voluminous and less diluted with water than the one used for the present observations. For example forty-one out of one hundred and seven infants one to twelve months old require more than three hours for their stomachs to empty after a milk feed, bread and milk or gruel and milk. When interpreting such results the psychological disturbance produced by performing the test must not be neglected for it was noticeable that six-months old infants and more particularly those of one year old had a greater distaste for milk feeds and the passage of the catheter into their stomachs than younger infants.

Conclusion

Gastric acidity during the first year of life shows a rapid increase in concentration (chart IV) with a probable increase in volume. At the end of this period the reaction of the stomach to a test-meal of milk closely resembles that of an adult, for the maximum and average values are almost identical in the two age groups. Accompanying the development of the digestive powers of the infant there is a diminution in the number of achlorhydric infants. The change applies to both true and false varieties of achylia, which is almost always transitory and not permanent; a fact which corresponds to the modern conception of gastric secretory function in adults (Chang, 1933; Morrison, 1938).

The behaviour of gastric secretion in infantile eczema and pyloric stenosis has also been studied. The results show that any disturbance that may be observed in these diseases is certainly not primary but secondary.

The present study on gastric acidity has been carried out under the auspices of the Kirk Duncanson Fellowship for Medical Research, The Royal College of Physicians of Edinburgh. Thanks are due to Professor Charles MacNeil and the obstetricians in charge of the wards of The Simpson Maternity Pavilion, The Royal Infirmary, Edinburgh, for the facilities to carry out the work. Not only has Professor MacNeil helped in this way but also by his constant interest and advice. Thanks are also due to Sister Taylor and Sister Stenhouse for their co-operation and technical assistance in performing the test-meals.

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BACILLARY DYSENTERY

BY

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The following communication is a survey of a group of patients with dysentery admitted to the Hospital for Sick Children, Toronto, from May 1939 to May 1941 inclusive. In all cases stool cultures were obtained showing a known pathogen. The report deals with clinical and bacteriological aspects of the disease. Brown et al. (1930) and Johnston et al. (1930, 1933) published a series of reports on the isolation of dysenteric micro-organisms from the stools of patients with ' intestinal intoxication.'

Clinical data. The present report deals with the investigation of twenty-nine infants and children with bacteriologically-proven dysentery. The ages of the group varied from two months to nine years of age. The main symptoms in order of frequency were as follows: fever (28), diarrhoea (22), vomiting (13), blood in stools (7), drowsiness (7), convulsions (5), and abdominal pain (5). None of the infants was receiving breast milk at the time of its illness. Twenty-eight of the twenty-nine patients lived in the city. Twenty-two of the patients were admitted during the months of August, September, October and November. Three patients were admitted in the month of May, three in December and one in March. There were sixteen males and thirteen females in the group. Twenty-three of the group had fever which varied between 100° and 104° F. In twenty-two of the twenty-nine patients the temperature fell by crisis in twenty-four to forty-eight hours after admission. The patients were treated in the main with fluids by mouth and a mixture containing bismuth salicylate and camphorated tincture of opium with chalk. Those patients who were more seriously ill received a continuous intravenous injection of glucose-saline and in some instances a blood transfusion. One patient received sulphathiazole and one patient received sulphaguanidine by mouth. All patients showed marked clinical improvement in the course of twenty-four to forty-eight hours.

Bacteriological data. The twenty-nine strains of dysentery cultures obtained from the stools of the patients were examined for morphology, for their reactions in various carbohydrate media and for their agglutination in specific rabbit sera. Twenty-three strains were found to be B. dysenteriae Sonne.

The remaining six strains were as follows : B. dysenteriae Flexner W (3), Flexner Y (1), Newcastle (2).

Discussion

Eighteen of the twenty-nine patients were two years of age and older and from a clinical standpoint it is possible that the disease was less severe than previously reported by Johnston et al. (1930) in younger age groups. In none of the groups did a death occur, in spite of the fact that only two patients received the sulphonamide group of drugs. In a discussion of the results of treatment in a group of patients with dysentery at the present time, it is important to mention the form of treatment employed. At present sulphaguanidine is being used in the treatment of dysentery with good results. This group of patients was treated with enteral and parenteral fluids, and it would be difficult to see from the results how they could be improved upon by the use of sulphaguanidine. Had this chemotherapeutic agent been used it would have been tempting to conclude that the drug was partially responsible for the rapid clinical recovery. The carrier state was not observed to be present in any case in this series. The investigation of the causes of dysentery in this group reveals that B. dysenteriae Sonne was by far the commonest offending micro-organism.

Summary

1. Clinical and bacteriological data are reported on twenty-nine patients with dysentery.

2. All patients recovered rapidly as a result of the administration of fluids.

3. Twenty-three of the twenty-nine patients were suffering from dysentery as a result of B. dysenteriae Sonne, three as a result of B. dysenteriae Flexner W, one as a result of B. Flexner Y and two as a result of B. Newcastle.

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THE RELATION OF MATERNAL DIET TO BREAST FEEDING

BY

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The importance of successful breast feeding in the growth, development and welfare of the infant is well recognized. Many observations have been made of the quality of the breast milk resulting from and dependent upon the mother's diet during lactation. It is the purpose of this communication to show how the prenatal diet can also affect the ability of the mother to nurse her infant successfully.

The details of a study of the effect of prenatal diet upon the mother and child have been published recently (Ebbs et al., 1941, 1942). Three groups of low-income expectant mothers attending the prenatal clinic kept diaries of their food intake for one week. These were analysed and three groups of patients were formed. One group found to have poor diets about the fourth or fifth month of pregnancy and who had low incomes were divided by leaving each alternate patient on her poor diet and by supplying the others with certain simple foods daily. Many patients were found to have moderately good diets and a fairly adequate income. They were given advice about improving their diet. Thus one group of one hundred and twenty women were left on their poor diets throughout pregnancy and are called the ' poor diet group.' Another group of ninety women who were found to have a poor diet were given extra food from the fourth or fifth month of pregnancy until the baby was six weeks old. They are referred to as the ' supplemented group.' A third group of one hundred and seventy women were given advice and their diets improved by education, forming a ' good diet group.'

The supplemented group were provided with the following foods daily: 30 oz. milk, one egg, 1 oz. cheese, one orange, 4½ oz. canned tomatoes, 2 tablespoons of wheat germ, and 1 viosterol capsule containing 2000 units of vitamin D. They were given advice about the other foods necessary to ensure a well-balanced diet, to be provided from their own income.

Analyses of food diaries kept by each patient at the beginning of the period of observation and again one month before confinement show the marked improvement in some of the important food elements brought about in the supplemented group by adding the above foods to a poor diet, and in the good diet group by education alone (table 1).

TABLE I

PERCENTAGE OF PATIENTS IN EACH GROUP ON BASIS OF DAILY CONSUMPTION OF PROTEIN, CALCIUM AND VITAMIN C (CITRUS FRUIT AND TOMATO)

		PROTEIN MORE THAN 80 GM.	CALCIUM MORE THAN 1·2 GM.	VITAMIN C MORE THAN 50 MGM.
Poor Diet	1st analysis	7	3	1
	2nd analysis	14	11	0
Supplemented	1st analysis	5	4	1
	2nd analysis	78	88	50
Good Diet	1st analysis	37	22	8
	2nd analysis	74	61	10

It will be noted that the percentage of patients in the poor diet group who were receiving more than the minimum requirements of protein, calcium and vitamin C was low and remained relatively low in the second analysis, whereas there was marked improvement in the second analysis of the supplemented and the good diet groups. The average vitamin B_1 content of the poor diets was 324 units daily, which was increased to 774 units when the extra food was supplied to the supplemented group

Observations of the whole course of pregnancy were made in order to compare the three groups of patients. The details of the obstetrical and paediatric findings have been published elsewhere (Ebbs, Scott et al., and Ebbs, Brown et al., 1942). During the prenatal period, during labour and during convalescence there were more complications in the poor diet group than in the other two groups. The general condition of the mothers in the better-fed groups was noticeably better and they were considered to be better obstetrical risks than those left on their poor diets. During convalescence in the hospital 12 per cent. of the patients in the poor diet group were considered to be in poor condition, compared with 4 per cent. of the supplemented group and 9 per cent. of the good diet group. The incidence of mastitis was twice as great in the poor diet group, compared with the supplemented group. The good diet group also showed a higher incidence of breast inflammation. The number of patients is too small to draw any definite conclusions, but mastitis is certainly a factor which interferes with successful breast feeding.

The supervisor of nurses at the maternity hospital where these women were confined has recorded in a large group of cases her findings with regard to the ability of the mother to nurse her infant (Ebbs, Brown et al., 1942). This was done without the diet groups of the patient being designated (table 2). Good rating indicates successful breast feedings. Fair rating is used when supple-

TABLE 2

THE ABILITY OF THE MOTHER TO NURSE THE INFANT IN THE HOSPITAL
(Ebbs, Brown et al., 1942)

	GOOD PER CENT.	FAIR PER CENT.	POOR PER CENT.
Poor diet	42	41	17
Supplemented diet	52	42	6
Good diet	49	43	8

mental feeding is necessary and the progress of the baby is not as rapid as normal. Poor indicates very slow progress, marked loss of weight on breast milk, poor supply of breast milk, or artificial feeding. When the mother returned for examination at the postnatal clinic, six weeks after delivery, the type of feeding and the progress of the baby was recorded. When the baby was brought for examination at the age of six months, the details of the duration of breast feeding were completed. Table 3 contains the percentage of babies in each group being breast fed up to the age of two weeks, whether still in the hospital or at home, and the incidence throughout the first six months of life. This is further illustrated in the graph (chart I).

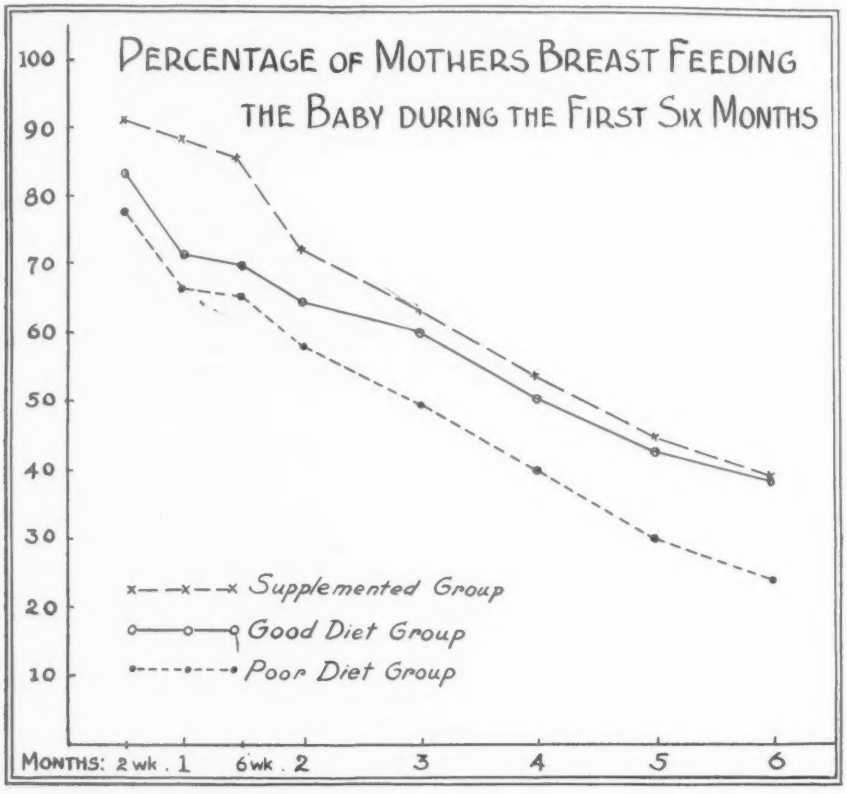

CHART I

Upon leaving the hospital, between the tenth and fifteenth day after delivery, there was a noticeable drop in the incidence of breast feeding, being more

marked in the poor and the good diet groups. After six weeks there was a marked drop in the number of babies in the supplemented group who were breast fed. The extra food being sent to this group was stopped when the baby was six weeks old. This seems to have influenced the ability of some of the mothers to continue the nursing period. Throughout the remaining period up to six months, the incidence of breast feeding was about the same in the supplemented and good diet groups, but was higher than in the poor diet group.

TABLE 3

INCIDENCE OF BREAST FEEDING UP TO SIX MONTHS
(Percentages)

	2 WEEKS	1 MONTH	6 WEEKS	2 MONTHS	3 MONTHS	4 MONTHS	5 MONTHS	6 MONTHS
Poor diet ..	78	67	65	58	49	40	30	24
Supplemented diet ..	91	89	86	72	63	54	44	39
Good diet ..	84	72	70	65	60	50	43	38

At six months of age the babies born of mothers in the supplemented and good diet groups were found to average a slightly higher weight than the babies of mothers in the poor diet group, and they had suffered from fewer illnesses. This might have resulted from better conditions at birth as a result of the mother's prenatal diet and from the increased incidence of breast feeding in the two well-fed groups.

Discussion

Robinson (1941) found in a study of the incidence of breast feeding in ten classes of the population that the greatest decline in breast feeding occurs in the first month among the wives of labourers in England, and that continued poverty lowers the ability of the mother to keep the baby on the breast through the first month. In another communication, Robinson (1939), states that the incidence of breast feeding is lowest in depressed industrial areas. That poverty is not the only factor in successful breast feeding is well recognized, since many who can and do afford a good prenatal diet do not nurse their infants, but poverty goes hand-in-hand with poor diet, which results in weakness and lack of proper health. By supplying food to the women in the study which has been described, it was noted that when the diet changed from a very poor one to a diet which at least contained the fundamentals of normal requirements, these women not only improved physically, but also mentally. Their attitude towards the outcome of the pregnancy, which formerly was one of apathy, soon became one of normal interest. This attitude seemed to be carried over into the postnatal nursing period. The sudden drop in the incidence of nursing in the supplemented group at six weeks might be explained by the change in mental attitude of the mother when the food was stopped, or it might have been the result of the sudden withdrawal of certain food factors which have

been suggested as influencing the secretion and the quality of breast milk. It is also recognized that nutrition is not the only factor concerned with successful breast feeding.

Summary

A comparison of the incidence of breast feeding in three groups of low-income class mothers has been made. The group which was supplied with extra food and the group which was educated to provide a good prenatal diet were more successful in nursing their infants than the mothers who had been left on poor prenatal diets. The effect of postnatal diet upon nursing was evident by a decrease in the percentage of breast-fed babies when extra food was stopped six weeks after the birth of the baby. The relation of poverty to poor prenatal diets and its effect upon the incidence of breast feeding and the development of the infant are pointed out.

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THE INCIDENCE AND MORTALITY OF BREAST- AND ARTIFICIALLY-FED INFANTS ADMITTED TO HOSPITAL WITH INFECTIONS *

BY

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Statements are often made and beliefs expressed about the relative values of breast and artificial feeding. In 1934, Grulee reported a study of some twenty thousand infants who had been followed in well-baby clinics in Chicago up to the age of nine months. The breast-fed babies were 48·5 per cent. of the total, while another 43·0 per cent. were partially breast-fed. There were approximately half as many infections in the breast-fed as in the artificially-fed group and only one-tenth the percentage of deaths. The results were definitely in favour of breast feeding. In analysing a large number of post-mortem records, Ebbs (1938) found that infants who died and were found to have otitis media and sinusitis were practically all artificially-fed at the time of onset of the infection.

During ward rounds in the Hospital for Sick Children, Toronto, the following questions were raised: (1) Are there more artificially-fed babies admitted to this hospital with infections than breast-fed babies? (2) Is the chance of survival from an infection greater in a breast-fed infant than in an artificially-fed infant? In order to try to answer these questions the records were examined of one thousand five hundred consecutive admissions of babies under twelve months of age with infections, admitted to the Hospital for Sick Children, Toronto.

Table 1 shows the age incidence of these children with infections. It will be noted that after the first two months the number in each month is fairly uniform.

TABLE 1

AGE INCIDENCE OF INFANTS STUDIED

AGE IN MONTHS	1	2	3	4	5	6	7	8	9	10	11	12
Number of babies	48	89	157	147	108	119	147	139	138	143	113	152

* Read at the Annual Meeting of the Canadian Society for the Study of Diseases of Children, Alexandria Bay, N.Y., 1939.

Table 2 gives the incidence of breast, artificial and mixed feeding. Two hundred and twenty-seven were breast-fed entirely or for at least eight months in those who were over this age. This number is 15·1 per cent. of the total. The artificially-fed group were those babies who had not been breast-fed or in the case of infants over six months who had not been breast-fed for more than six weeks. Eight hundred and thirty-six (55·7 per cent.) were in this group. Four hundred and thirty-seven (29·1 per cent.) had been breast-fed for at least six weeks and then artificially-fed up to the time of admission. There were more artificially-fed infants admitted to the hospital with infections than breast-fed infants with infections. In order to determine the incidence of breast feeding amongst the class of babies from which the hospital admissions were drawn, the findings of Dr. C. B. Shillington, who attended well-baby clinics in different sections of the city and recorded the feeding of each child attending on that day, have been used. He found that 35·6 per cent. were, or had been, breast-fed, 28·1 per cent. were artificially-fed and 36·2 per cent. were breast-fed for a reasonable time and then artificially-fed.

TABLE 2
INCIDENCE OF BREAST FEEDING IN HOSPITAL ADMISSIONS COMPARED WITH BABIES ATTENDING WELL-BABY CLINICS

	HOSPITAL INFANTS WITH INFECTIONS PER CENT.	INFANTS ATTENDING WELL-BABY CLINICS PER CENT.
Breast-fed	15·1	35·6
Breast-fed and then artificial feeding	29·1	36·2
Artificial feeding ..	55·7	28·1

From table 3 it will be seen that respiratory infections are responsible for the majority of admissions to the hospital of babies up to one year. 73·7 per cent. were respiratory and associated infections, while 20·9 per cent. had gastro-

TABLE 3
MORTALITY OF BABIES WITH RESPIRATORY INFECTIONS IN RELATION TO TYPE OF FEEDING

	NUMBER OF CASES	DEATHS	PER CENT.	
Breast-fed	190	28	14·7	12·7
Breast-fed and then artificially-fed	337	39	11·5	
Artificial feeding	579	92	15·9	

MORTALITY OF BABIES WITH GASTRO-INTESTINAL INFECTIONS IN RELATION TO TYPE OF FEEDING

Breast-fed	17	4	23·5	13·5
Breast-fed and then artificially-fed	79	9	11·4	
Artificial feeding	218	33	15·1	

MORTALITY OF BABIES WITH MISCELLANEOUS INFECTIONS IN RELATION TO TYPE OF FEEDING

Breast-fed	20	10	50·0	36·5
Breast-fed and then artificially-fed	21	5	23·8	
Artificial feeding	39	12	30·7	

intestinal conditions such as intestinal intoxication, infectious diarrhoea and diarrhoea not associated with respiratory infection. Only 5·3 per cent. had other infections such as abscess, infections of the skin or genito-urinary infections.

Of the breast-fed babies 83·7 per cent. had respiratory infections compared with 69·2 per cent. of the artificially-fed and 77·1 per cent. of the infants with mixed feeding. Only 7·5 per cent. of the breast-fed group had gastro-intestinal infections compared with 26 per cent. of the artificially-fed and 18·1 per cent. who had breast and then artificial feeding. The percentage of deaths among totally breast-fed babies was slightly higher than in the other two groups. There were forty-two deaths in 227 breast-fed babies admitted with infections, a percentage mortality of 18·5. However, this is only 18·1 per cent. of all the deaths which occurred in this series. There were 137 deaths in 836 artificially-fed babies, or 16·4 per cent. This is 59·1 per cent. of all deaths. The mortality in the babies entirely breast-fed and those who had been breast-fed an appreciable length of time was 14·3 per cent. as compared with 16·4 per cent. of those artificially-fed throughout (table 4).

TABLE 4

MORTALITY IN 1500 INFANTS WITH INFECTIONS

FEEDING	CASES		DEATHS		
	NUMBER	PER CENT. OF TOTAL	NUMBER	PER CENT.	PER CENT. OF TOTAL DEATHS
Breast	227	15·1	42	18·5 } 14·3	18·1
Breast and artificial	437	29·1	53	12·1 }	22·8
Artificial	836	55·7	137	16·4	59·1
Total	1500		232	15·4	

Summary

In reviewing the case histories of one thousand five hundred infants under one year of age, admitted to the Hospital for Sick Children, Toronto, with infections, during three and a half years, evidence was found that fewer breast-fed babies were admitted with infection than artificially-fed babies. The incidence of breast feeding among the one thousand five hundred admissions with infections was less than half the incidence of breast feeding in the well-baby clinics in the city. Respiratory infections were found more frequently than other infections. The incidence of gastro-intestinal infections was lower in the breast-fed babies. The percentage mortality was slightly higher in the breast-fed group.

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CYSTIC FIBROSIS OF THE PANCREAS *

BY

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Cystic fibrosis of the pancreas has been found relatively frequently in post-mortem examinations of dystrophic infants at the Hospital for Sick Children, Toronto. Nineteen cases have been recognized during the past twenty years, and eleven of these during the past year and a half. Up to the present, in our experience, this condition is a pathological entity diagnosed for certain only after microscopic examination of the pancreas has been carried out. In addition pathological examination has revealed moderately constantly associated conditions in the patient, namely, bronchiectasis, lung abscess, metaplasia of epithelium and fatty liver.

An analysis of the clinical records of the nineteen cases has revealed an almost constant train of events but, as aptly stated by Blackfan and May (1938), ' the clinical manifestations were limited in variety but were so common to many disorders in infancy that it has not been possible to determine accurately the dependable diagnostic features.'

There were nineteen cases with the ages ranging from two to twenty-one months at the time of post mortem. Female sex predominance was observed, being found in eleven of the nineteen. Six of seven cases over six months of age were females. The social status of the whole group was poor. A marked irregularity of incidence has especially been noted, five cases being found in the years 1923 to 1925 and fourteen from 1937 to 1941, with none in the intervening period. The period of the year during which the mother was pregnant and the age of the parents showed no constant trend.

The symptoms are of two groups, nutritional and respiratory. The symptoms referable to nutrition were failure to gain or loss of weight, vomiting, loose and frequent stools, colic and abdominal distension. In most of the cases, particularly those under six months of age, these symptoms were present from birth, in spite of breast feeding being used for all or a large proportion of the time in fourteen cases. Low fat feedings were used in only two cases. Cod-liver oil or its equivalent in amounts considered adequate for vitamin A supplement were given in at least nine cases. Respiratory symptoms were cough, wheezing, rapid breathing and cyanosis. Fourteen patients showed

* Read at the Eighteenth Annual Meeting of the Canadian Society for the Study of Diseases of Children, Brockville, Ontario, June 14, 1941.

respiratory symptoms and in three these symptoms were observed from within a few days of birth.

Signs of malnutrition were observed in all. Many showed abdominal distension, hepatic enlargement, and presented the picture of moderate to severe chronic nutritional disturbance. One third were more than 40 per cent. below the average weight.

Physical signs of lung involvement such as bronchitis, collapse and consolidation of the lung, bronchopneumonia and bronchiectasis were present on admission or during the period of observation in all the cases.

X-ray examination of the lung showed changes, among which were increased linear markings, fibrosis, pulmonary collapse, shift of mediastinum and consolidation. In spite of chemotherapy and bronchoscopic suction the inflammatory process in the lung progressed to a more pronounced state, ending with the death of the patient.

Staphylococcus aureus was cultured from the lung in all but one case, in which no culture was made. Secondary anaemia was present in many but was not a constant feature. Pyuria was found twice.

Post-mortem examination revealed extensive changes in both pancreas and lung in eighteen of the nineteen cases. In one case the lung changes while of the same nature were only minimal in extent. Although in the cases encountered some years ago the gross examination of the pancreas did not suggest anything abnormal, more recently gross changes have been recognized, doubtless due to the fact that they are being looked for. These consisted chiefly of an increase in the firmness of the gland and a variation in the size and shape of the individual lobules, which tended to be spherical rather than of the normal diamond shape. Attempts to trace out the pancreatic ducts in the gross met with little success, but this need not necessarily be interpreted as due to malformation of the ducts.

Microscopically all degress of fibrosis of the pancreas were found from delicate bands of interlobular connective tissue (fig. 1 A) to a dense, diffuse fibrosis (fig. 1 F). Likewise the changes in the acini varied from a mild dilatation to huge cysts lined by a cuboidal or flattened epithelium and containing varying amounts of pink-staining material which sometimes had a concentric arrangement (fig. 1 B to E) or may even have undergone calcareous degeneration. In one pancreas (fig. 1 F) there were numerous large irregular cystic spaces in the head of the gland suggestive of malformation of the duct with partial obstruction and dilatation. The islands did not appear to be affected by the process.

The lung changes were striking and presented a great similarity from case to case. Perhaps the most outstanding feature was the plugging of numerous bronchi and bronchioles with thick, tenacious, greenish or yellowish, purulent exudate (fig. 2 A and B). Other lesions included widespread bronchiectasis of smaller bronchi and bronchioles (fig. 2 A, B, C) and multiple abscesses which in some instances perforated the pleura (fig. 2, D 3) giving rise to empyema. In most cases, also, there were areas of recent lobular pneumonia (fig. 2, D 1 and 2). In some cases the bronchiectatic cavities were partially lined by squamous

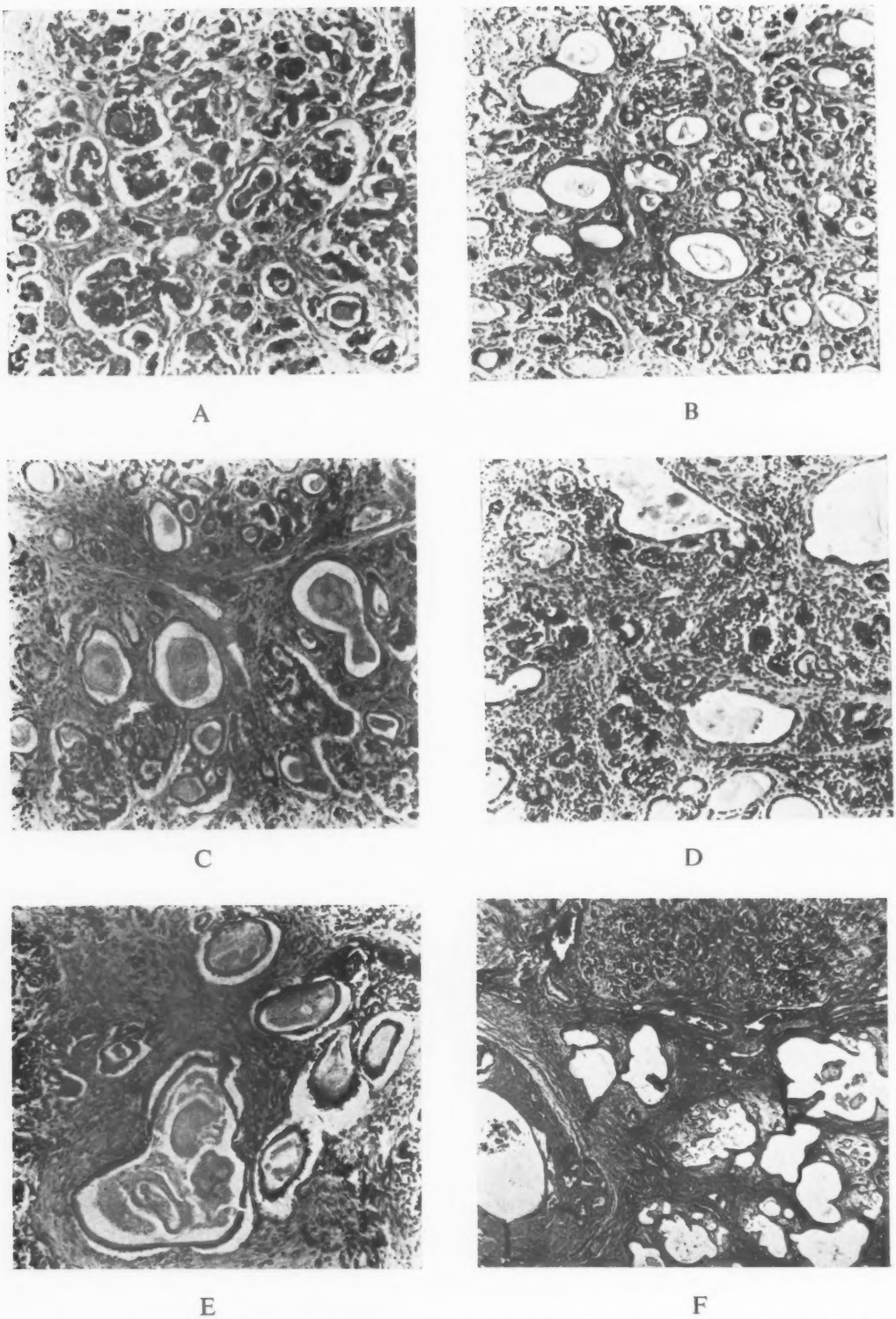
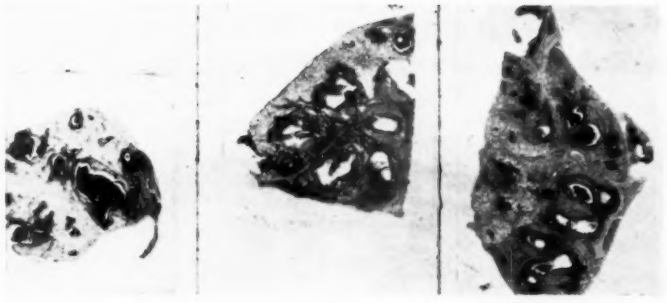


FIG. 1.—Photomicrographs of pancreas from six different patients with cystic fibrosis of pancreas. Ages at death ranged from 3 months to 21 months. All showed chronic lung changes. Ages in months: A. 21, B. 5½, C. 9½, D. 3, E. 5½, F. 3.

Hematoxylin and eosin, A to E×110 F×25.

1 2 3

A

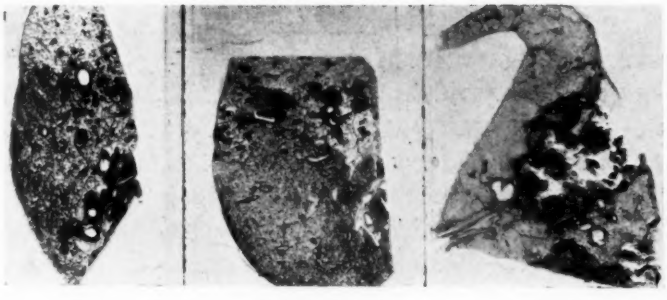


1 2 3

B

1 2 3

C



1 2 3

D

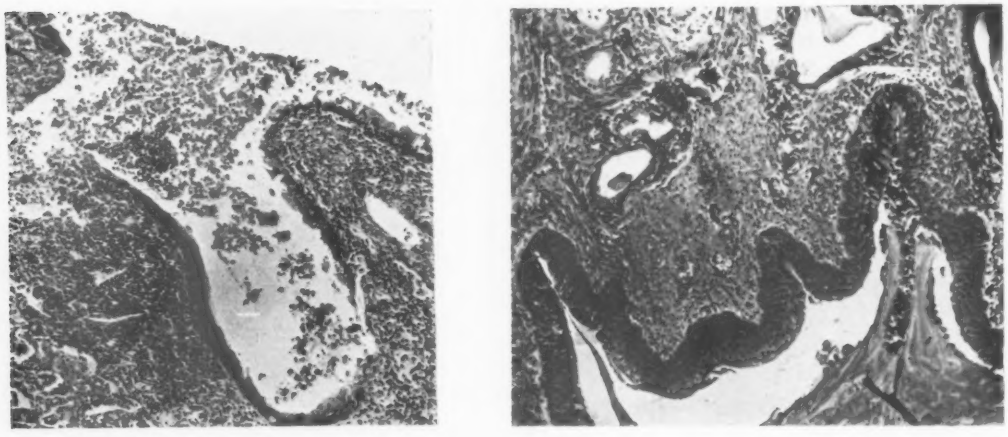
FIG. 2.—Sections of lung from six different patients with cystic fibrosis of pancreas.

A. Infant of 10 months. B. Infant of 21 months. Pancreas shown fig. 1 A.
C. Infant of 5½ months. Pancreas shown fig. 1, B. D. 1. Infant of 3 months.
D. 2. Infant of 3 months. Pancreas shown fig. 1 D. D. 3. Infant of 7 months.
Hematoxylin and eosin × 1·8.

epithelium (fig. 3 A). In others there was squamous metaplasia of the epithelium of the trachea (fig. 3 B). As pointed out above the predominating organism was staphylococcus aureus.

Although the outstanding changes were found in pancreas and lungs another almost constant finding was the presence of fat in varying amounts in the liver cells.

The sequence of events so far as the lung is concerned appears to be as follows: Whatever the cause of metaplasia of tracheal and bronchial epithelium the loss of ciliary activity results in a sort of physiological obstruction to the removal of secretion from the bronchi and bronchioles. As these secretions, infected usually by staphylococci, continue to accumulate in the bronchi the



A B

FIG. 3 A.—Photomicrograph of wall of bronchiectatic cavity (fig. 2 C) showing epithelial metaplasia. For pancreas see fig. 1 B.

FIG. 3 B.—Photomicrograph of wall of trachea from 3 months old infant, showing epithelial metaplasia, and dilated glands in mucosa.
For pancreas see fig. 1 F. Hematoxylin and eosin × 75.

combination of pressure on the mucosal lining plus the toxic action of the bacteria frequently results in varying degrees of ulceration of epithelium with damage to the supporting structures, with varying degrees of dilatation of the bronchial tree. Strangely enough, these changes may be extensive in a given lobe of the lung and show evidence of much chronicity without any appreciable involvement of the surrounding lung parenchyma (fig. 2 D, 1 and 2). Usually, however, by the time the case comes to autopsy one or more lobes show quite extensive recent lobular pneumonia which may be interpreted as the last link in the long chain of events leading ultimately to the death of the patient.

Wolback and Howe (1925) demonstrated experimentally that vitamin A deficiency in the guinea pig and albino rat brought about a substitution of stratified keratinizing epithelium for normal epithelium. Similar metaplasia in infants was reported by Blackfan and Wolback (1933) describing the picture of vitamin A deficiency where they observed metaplasia of epithelium, particularly of the respiratory tract associated with pulmonary infections and of the pancreas where the picture was one of fibrocystic disease. They stated

that at first they regarded the pancreatic change as one of vitamin A deficiency, but since it was observed without other evidence of vitamin A deficiency and vitamin A deficiency might be present without pancreatic change the two were not necessarily connected. Blackfan and Wolback (1933) and later Blackfan and May (1938) expressed the view that the pancreatic change was due to the production of an abnormal secretion which inspissates in the ducts, leading to destruction and atrophy of ducts and acini. This may be responsible for the failure to utilize fats and vitamin A. Andersen (1938, 1939) observed the same pathological changes in a series of cases and stated that the changes in the lung and epithelium in other parts of the body may be secondary to a lack of vitamin A resulting from poor fat absorption as a consequence of primary change in the pancreas, because if no fat is absorbed vitamin A is not absorbed either. She felt that the pancreatic abnormality was probably a congenital defect because symptoms frequently commence at birth. Other possible explanations given by her were foetal inflammation of the pancreas or vitamin A lack in the mother. It is agreed by these authors that the lung changes are due to a metaplasia of bronchial epithelium with a lack of secretion and loss of ciliary action allowing infection and stagnation to take place in the bronchial tree and alveoli.

That lack of vitamin A ingestion is not the predisposing cause is shown by the finding that in at least nine of the present cases amounts of vitamin A considered adequate had been supplemented to the usual milk diet. No data are available on the vitamin A intake of the mother. However, figures from the Ontario Government on employment have been considered and this bears no constant relation to the incidence of this disease. Ebbs (1941), in a survey of the diets of pregnant women found that deficient diets were common during 1938–39 and up to the fall of 1940, when rather suddenly the deficient diet almost ceased to exist among the pregnant women in the clinic. It will be interesting to see if the incidence of this disease falls off.

Vitamin A deficiency as a result of poor absorption due to a primary pancreatic lesion will in due time lead to metaplasia of the bronchial epithelium and the respiratory symptoms. However, this sequence of events could hardly be present in three of our cases in which the respiratory symptoms were present within a few days of birth. A case of xerophthalmia in an infant seven-and-a-half months of age was observed by us. Sobee had been employed in feeding this patient from three weeks of age, with viosterol as a supplement. The earliest symptoms observed four months later were a head cold and stationary weight. Even at seven-and-a-half months there was no bronchopneumonia or bronchiectasis. Eight of the present patients came to post mortem at four months of age or under and all were fed on breast milk or whole-milk feedings. This is a short time for the changes to occur due to vitamin A lack after birth. It certainly would appear in these that the lung changes had begun prior to birth. This suggests that vitamin A lack in the mother is a probable cause of this trouble. In support of this, all of the patients had a poor social background.

The sequence of events in this syndrome can occur in at least two ways: (1) the condition is primarily in the pancreas as an inherited or congenital or acquired defect; or (2) the condition in the child is the result of some defect in the diet of the mother or her ability to pass vitamin A to the foetus.

(1) With a defect of the pancreas there is poor absorption of fat soluble vitamin A, followed by metaplasia of epithelium, particularly seen in the

bronchial tree. This change causes poor ciliary action of bronchial epithelium, stagnation of infection followed by bronchiectasis.

(2) If there is primarily a defect in the vitamin A supply from the mother, then at birth the pancreas and bronchial epithelium might both be affected. Due to poor pancreatic function vitamin A absorption is interfered with causing further changes in the lung with a result similar to that described above.

Staphylococcal infection of the lung occurs in practically all of these cases. In examining the pneumonia records for the hospital, of 184 cases of infants under two years of age, it is found that the staphylococcus is one of the causative organisms in forty-two, or twenty-five per cent. It is interesting to speculate about the factor which predisposes to staphylococcus infection in this condition.

Regarding diagnosis, from our experience to date this has been accurately established only at post mortem. The diagnosis has been made, with a query in a few ante mortem, but in one of these no changes were found in the pancreas and the lung showed the usual type of bronchopneumonia seen in infants.

May and McCreary (1940, 1941) using the barium sulphate meal, glucose tolerance test, stool fats estimation and vitamin A absorption test state that none of these tests were specific for the diagnosis of coeliac disease in differentiating it from other conditions (including cystic fibrosis of pancreas) which produce coeliac-like symptoms. Andersen states that this condition can be differentiated from coeliac disease by aspiration of duodenal contents and analysing for trypsin, lipase and amylase. These are absent in cystic fibrosis of the pancreas but not in coeliac disease.

It is possible that patients with milder forms of this condition recover but from our experience to date the prognosis is very unfavourable.

In treatment Andersen has advised that the patients be fed 20 to 40 per cent. more than the average required calories because she feels in that way with partial absorption the requirements will be met. In addition large amounts of vitamin A are given and pancreatin is mixed with the feeding. She feels that she has improved certain patients by this routine.

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A STUDY OF THE QUANTITATIVE FRAGILITY TEST IN CHILDREN

BY

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Although in recent years great advances have been made in the classification and diagnosis of the anaemias, those of haemolytic origin still present unusual difficulties. The etiology of many of these is unknown and they form a composite group from which as investigations proceed clinical entities are separated. Acholuric jaundice is one such entity. The first description of the syndrome was given by Minkowsky (1900) who emphasized the familiar nature of the disease characterized by anaemia, jaundice, excess urobilinuria and increased bile pigment in the blood.

In 1907, Chauffard noted that in this condition the erythrocytes in comparison with those of normal blood showed a diminished resistance (or increased fragility) to saline, and this for a time came to be recognized as pathognomonic of the disease. Following on this discovery the fragility of the red cells was determined by various methods, all of them qualitative. Such a test is still employed. The method most commonly in use consists in the preparation of varying strengths of saline ranging from 0·38 per cent. to 0·60 per cent. at 0·02 per cent. intervals. The accuracy of the sodium chloride solution should be verified by standardizing with a silver nitrate solution of known strength. Approximately equal quantities of the cells to be examined are added to each of the saline dilutions, the resulting solutions being thoroughly mixed and allowed to stand overnight. The supernatant fluid in the lower dilutions becomes tinged with pink due to the freeing of haemoglobin from the lysed cells and the degree of haemolysis is estimated merely by noting the depth of this colour and the amount of sediment remaining in the bottom of the tubes. Normally, haemolysis is complete in a solution of 0·38 per cent. saline, and is just perceptible in a solution of 0·48 per cent. Where increased fragility of the red cells is present, haemolysis is apparent in more concentrated solutions.

The test described is rough and a more delicate method of demonstrating minor departures from normal is desirable, especially because fragility may be increased in certain acute haemolytic anaemias and returns to normal when haemolysis ceases (Parsons and Hawksley, 1933), and acholuric jaundice may exhibit normal erythrocyte fragility (Dawson, 1931 ; Gännslen, 1922). Gännslen quotes a family in which acholuric jaundice occurred, 10 per cent. of those affected showing no alteration in erythrocyte fragility, but details of the method

of estimation are not given. With a qualitative method, the presence of a small number of unduly fragile cells may not be recognized. Some cases of haemolytic anaemia which do not fall into any recognized group may exhibit a slight increase in red cell fragility which remains undetected by a rough test.

In 1923 Simmel published an account of a quantitative method which he had evolved. The test consists of a series of erythrocyte counts, using varying strengths of a specially prepared solution as the diluting agents, the difference in the counts indicating the number of cells haemolysed. This method has been employed, with minor modifications, by Whitby and Hynes (1935) in healthy adults, but few observations have been made in children. In order to define the limits of normality in children and to attempt to assess the value of the method, quantitative fragility tests have been carried out in a series of normal young children and in certain cases of diseases of the blood, especially the haemolytic anaemias.

Method

The method used was based on that described by Simmel. The fluid which he employed in preparing the diluting solutions had the same osmotic pressure as blood plasma, and the salts present were in the same proportion as they occurred in the blood, viz:—

Sodium chloride	8·2 gm.
Potassium chloride	0·2 gm.
Magnesium chloride	0·2 gm.
Calcium chloride	0·2 gm.
Acid sodium phosphate	0·2 gm.
Sodium bicarbonate	0·08 gm.
Distilled water	1,000 c.c.

As the excessive haemolysis occurring in haemolytic anaemias has been shown by Bergenhem and Fähraeus (1936), amongst others, to depend not on the salts present in the plasma but on the presence of lysolecithin, the estimation of the fragility of the cells in any solution of salts is purely an artificial test. Consequently there appears to be no reason for employing a haemolysing fluid which necessitates such elaborate preparation, and the solutions suggested by Whitby and Hynes were employed, namely varying strengths of sodium chloride. If the test were to be employed routinely, it would become too laborious if the degree of haemolysis occurring in numerous dilutions had to be estimated, so eight dilutions at 0·05 per cent. intervals, ranging from 0·35 per cent. to 0·70 per cent. were considered adequate for clinical work. The solutions were standardized with 0·15 per cent. silver nitrate and were found to keep in tightly stoppered bottles for one month. Capillary blood was taken from a puncture on the heel, care being taken that no pressure was exerted at the site of the wound. Dilutions of 1 in 200 were made with the various sodium chloride solutions in red cell pipettes, which then stood at room temperatures for one hour. The non-haemolysed erythrocytes in three samples of each dilution were then counted in a Thoma counting chamber, the averages being taken as the final readings. An erythrocyte count of the patient's blood was also done using Hayem's diluting fluid, and the number of cells haemolysed in the several dilutions expressed as a percentage of the total erythrocyte count.

Normal erythrocyte fragility

For the study of the average erythrocyte fragility and the limits of normality, fifty children who had been admitted to hospital suffering from complaints other than those related to the haemopoietic system were selected. In each instance the estimations were carried out when the child was fit for dismissal from hospital and in none of the cases was there any known family history of diseases of the blood. The ages of the children ranged from two weeks to twelve years, and the results, which are recorded in age groups in table 1, show the percentage of red cells haemolysed in the various dilutions.

TABLE 1

INDICATING THE AVERAGE ERYTHROCYTE FRAGILITY IN THE VARIOUS AGE GROUPS EXAMINED

AGE GROUP (YEARS)	NO. OF CHILDREN	ERYTHROCYTE HAEMOLYSIS PER CENT.							
		SALINE : GM. PER CENT.							
		0·35	0·40	0·45	0·50	0·55	0·60	0·65	0·70
2/52–3/12 ..	4	98	89	69	28	3	0	0	0
3/12–6/12	6	95	82	89	14	1	0	0	0
6/12–1	8	93	82	37	17	1	0	0	0
1–2	7	94	83	47	10	0	0	0	0
2–6	6	94	81	56	11	0	0	0	0
6–12	19	96	77	46	12	0	0	0	0
Average of 50 children ..		95	81	47	14	1	0	0	0

The average degree of haemolysis occurring in the various dilutions, charted as a curve (fig. 1) corresponds closely with the average curve compiled

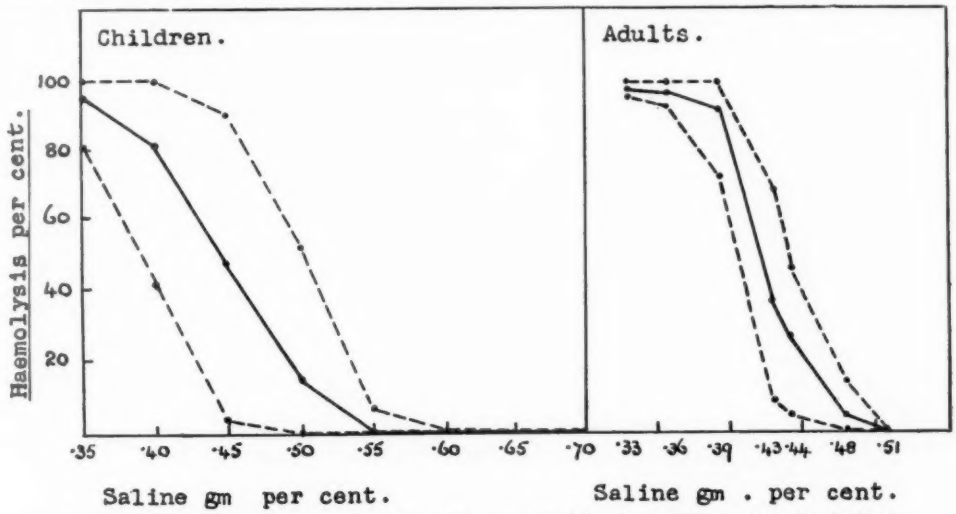

FIG. 1.—Comparing the limits of erythrocyte fragility in children with the limits in adults (Whitby and Hynes).

by Whitby and Hynes for adults. For comparison with their results, the degree of variability was similarly calculated by using 4 × standard deviation. The range calculated in this way from a small series of figures will include most possible results. Eleven of the children showed erythrocyte haemolysis of over 20 per cent. in the 0·50 per cent. solution. This increased degree of haemolysis could not be explained and occurred irrespective of age although two children below three months were included.

A study of the foregoing series of results shows the range of dilutions in which partial haemolysis occurs to be relatively constant in the groups of children examined, though there is a tendency for haemolysis to extend into the more concentrated solutions in the youngest age group, i.e. two weeks to three months. This apparent increase in erythrocyte fragility in early infancy may be a partially erroneous impression as the number of children in the youngest age groups was smaller than in the older groups, but the possibility that the age factor might influence the erythrocyte fragility in infancy was considered. An increase in fragility at birth which gradually diminishes during the first week of life, has been shown to occur by Goldbloom and Gottlieb (1929). In order to discover how long this increase persists, qualitative fragility tests were made on four apparently healthy infants at two-day intervals from birth till two weeks old. There was no excessive jaundice and the erythrocyte counts were within normal limits for that age. The averages of the results obtained in these four cases are given in table 2.

TABLE 2

SHOWING THE AVERAGE DEGREE OF ERYTHROCYTE HAEMOLYSIS IN VARIOUS SALINE SOLUTIONS IN FOUR INFANTS AT TWO-DAY INTERVALS FROM BIRTH UNTIL TWO WEEKS OLD

DAY OF LIFE	ERYTHROCYTE HAEMOLYSIS PER CENT.							
	SALINE GM. PER CENT.							
	0·3	0·40	0·45	0·50	0·55	0·60	0·65	0·70
1	79	77	64	46	29	0	0	0
3	79	73	41	38	10	0	0	0
5	91	81	34	40	20	0	0	0
7	83	68	38	22	20	0	0	0
9	90	72	52	24	20	0	0	0
11	91	79	50	14	10	0	0	0
13	92	80	59	12	5	0	0	0

At birth there is a decrease in the degree of fragility of the red cells in the lower concentrations of saline, and a tendency for an increase in haemolysis to occur in the more concentrated solutions, that is, there are some cells more resistant than usual and others more fragile. On subsequent days the degree of haemolysis gradually altered until by the eleventh day of life it approached that found in older children. It may be concluded that there is no correlation

between the variation of the erythrocyte fragility and the age of the child beyond, say, the first two weeks of life.

That carbon dioxide will increase the fragility of the red cells has been shown by Whitby and Hynes, who estimated the fragility of venous and arterial blood, and of blood saturated with carbon dioxide. Erythrocyte fragility was therefore estimated in the capillary blood from the heel of three healthy children, (*a*) before, and (*b*) after inhibiting venous return for two minutes. The resulting average alteration in fragility is indicated in table 3. There is both a quantitative and qualitative increase in fragility during venous stasis, more cells being haemolysed in the higher dilutions and haemolysis extending to the lower dilutions. The results of this experiment show that in the estimation of erythrocyte fragility, the findings may be influenced by other factors than those of pathological significance. False positive results may be obtained if great care is not taken to avoid venous stasis when collecting the samples of blood, and in children this is specially important as venous congestion can be more easily produced in the limb of a child than of an adult.

TABLE 3

SHOWING THE AVERAGE ALTERATION IN ERYTHROCYTE FRAGILITY IN THREE CHILDREN FOLLOWING VENOUS STASIS

CAPILLARY BLOOD	ERYTHROCYTE HAEMOLYSIS PER CENT.							
	SALINE GM. PER CENT.							
	0·35	0·40	0·45	0·50	0·55	0·60	0·65	0·70
(*a*) Before venous stasis	94	90	50	17	0	0	0	0
(*b*) After venous stasis	96	97	93	48	20	0	0	0

Fragility tests in children with non-haemolytic anaemia

The material investigated under this heading consists of twelve cases of iron-deficiency anaemia, three of thrombocytopenic purpura and one each of lymphatic leukaemia, Banti's syndrome and lymphadenoma. The results are shown in table 4.

The only case in which any material departure from the normal was encountered was the child aged six years with lymphatic leukaemia. The reticulocyte count was 1·4 per cent. and no urobilin was found in the urine. There was an increase in the degree of haemolysis although the range was normal.

Fragility tests in children with haemolytic anaemia

It is in this group that a study of the quantitative fragility test becomes of the greatest interest and in which it might be of the greatest help in diagnosis. Two cases of acholuric jaundice were investigated by the quantitative method,

both before and after splenectomy and the results obtained are most conclusive, a marked increase in erythrocyte fragility being present in both cases, which became less marked following splenectomy. Although the qualitative test in such cases also left no room for doubt, the quantitative test has a greater finality. In one case of a mild haemolytic anaemia corresponding to the type referred to as von Jaksch's, the fragility was within normal limits.

TABLE 4

INDICATING THE QUANTITATIVE FRAGILITY TESTS IN VARIOUS DISEASES AND IN TWO UNCLASSIFIED CASES (G.H. and M.F.)

	ERYTHROCYTE HAEMOLYSIS PER CENT.							
	SALINE GM. PER CENT.							
	0·35	0·40	0·45	0·50	0·55	0·60	0·65	0·70
Normal children	95	81	47	14	1	0	0	0
Iron-deficiency anaemia (average of 12 cases)	97	87	49	13	6	0	0	0
Thrombocytopenic purpura (average of 3 cases)	97	96	37	12	10	0	0	0
Banti's syndrome	97	80	40	10	6	0	0	0
Lymphatic leukaemia	100	100	92	90	25	0	0	0
Lymphadenoma	96	97	50	10	0	0	0	0
G.H. (during exacerbation) ..	98	97	96	14	22	14	20	14
1 year following exacerbation ..	98	99	97	70	33	30	15	10
M.F. (during 2nd exacerbation)..	94	80	80	35	23	20	0	0
Following 2nd exacerbation ..	99	82	79	30	20	23	0	0
Following 3rd exacerbation ..	98	98	90	82	50	20	0	0
Latent period	99	99	91	80	63	30	0	0

Three cases of congenital haemolytic anaemia were studied. All were admitted to hospital during the first week of life. An extreme degree of anaemia, recticulocytosis, splenomegaly and excessive urobilinuria indicated that pathological haemolysis was occurring. Quantitative fragility tests done in the second week of life gave normal results. The actual figures of these tests are omitted for the sake of brevity.

Two further cases of haemolytic anaemia which were studied have remained unclassified. Although the quantitative fragility test in both cases complicated rather than simplified any attempts made to classify them, it did reveal an increase in fragility which might have been overlooked had a qualitative method of estimation been employed. The results of erythrocyte fragility estimations in these children are shown in table 4.

G.H., aged 10 years. Nothing relevant in family history. No previous illnesses. On admission she gave a history of increasing weakness and pallor during the previous six weeks, and complained of abdominal pain. Blood examination on admission was as follows : red blood cells 890,000 per c.mm., haemoglobin 30 per cent. (Sahli), reticulocytes 36 per cent. Qualitative fragility test showed no apparent haemolysis in solutions beyond 0·52 per cent. sodium chloride, whilst

a quantitative test revealed haemolysis (14 per cent.) in a solution of 0·70 per cent. sodium chloride. Urine examination showed urobilin ++. No immediate improvement followed transfusion of paternal blood, but haemolysis ceased spontaneously eleven days later.

One year later, when the girl was apparently well, the reticulocyte count being normal and tests for urobilin being negative, a quantitative fragility test showed that the increase in fragility had persisted, haemolysis still being apparent in a 0·70 per cent. solution.

The complexity of the haemolytic anaemias becomes evident when any attempt is made to classify this case. A history of a relatively sudden onset accompanied by abdominal pain is suggestive of Lederer's anaemia. The erythrocyte fragility, however, which may be temporarily increased while haemolysis is occurring in this type of anaemia rapidly returns to normal with cessation of haemolysis. In the absence of evidence of increased fragility as shown by the quantitative test, this child would have been classed in this group. The persistent increase in cell fragility suggests a diagnosis of acholuric jaundice, though there is nothing in the family history to suggest this. It is conceivable that cases of slight increase in fragility such as shown by this child but with no clinical evidence of excessive haemolysis may exist. Such cases would pass unrecognized unless a quantitative fragility test was done.

M.F. First child. Nothing relevant in the family history. She was first admitted at the age of thirteen months on account of severe anaemia, and at that time was found to have a congenital heart lesion. Blood examination showed severe anaemia with normal colour index and marked reticulocytosis. A blood transfusion was given and she was dismissed home on ferrous sulphate which was given at intervals throughout the course of her illness. Exacerbations of the anaemia occurred at the ages of seventeen months, two years three months and two years nine months. On each occasion she responded to blood transfusion, though at no time did her reticulocyte count fall within normal limits, and the presence of urobilin was noticed on several occasions. During her third admission, cyanosis and digital clubbing were evident and a skiagram of the lung showed marked congestion. The spleen was at no time palpably enlarged and her Wassermann reaction was negative. A fourth exacerbation occurred at three-and-a-half years, which did not respond to repeated blood transfusions, and the child died.

Post-mortem examination revealed a congenital heart lesion (pulmonic stenosis), but threw no light on the etiology of the anaemia.

Quantitative fragility tests done during and after the first three exacerbations of the anaemia, and subsequently during a latent period, indicated an increase in erythrocyte fragility which appeared to progress with the increase in cyanosis.

Conclusions

Quantitative fragility tests carried out on normal children are comparable with those obtained in adults except in the first week of life, when there is a slight decrease in haemolysis in the lower saline concentrations and a tendency for haemolysis to extend to the more concentrated solutions. The test will reveal alterations in erythrocyte fragility which would be overlooked by a qualitative estimation.

Cyanosis, with a rise in the carbon dioxide content of the blood, increases not only the degree of haemolysis in the various saline dilutions but also to a slight extent the range of solutions in which haemolysis occurs. Consequently the importance of the test depends as much on the range of solutions in which haemolysis occurs as on the degree of haemolysis in the various dilutions.

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CASE REPORT

TWO CASES OF GLYCOGEN DISEASE

BY

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In 1929, von Gierke described two cases of a previously undefined condition which he called 'Hepatonephromegalia glycogenica.' In a paper in 1931 he used the name 'Thesaurismosis glycogenica' and this term has since been used by Spanish authors (Jiménez Diaz et al., 1940). It is now usually called 'Glycogen disease,' 'Glycogen storage disease,' or 'von Gierke's disease.' Cases probably of this condition had been described previously by Wagner and Parnas (1921) and Snapper and van Creveld (1928). Full reviews of the subject have been published by Ellis and Payne (1936), van Creveld (1939), and Atkinson (1939).

Two cases are here described. An earlier report on the first was made by Warner (1933).

Case 1. Female, aged eight years.

HISTORY. The child was first seen at the age of two years with jaundice and an enlarged abdomen. For ten days she had had a cough and for seven days mild jaundice. The stools were white and the urine dark orange coloured. The liver extended ½ inch below the umbilicus. There were two dilated veins on the abdominal wall.

The jaundice passed off gradually and the liver was found to extend to 1 inch above the umbilicus. Since then the liver has gradually become larger and she has had repeated attacks of bronchitis.

At the age of six-and-a-half years, her height was 39½ inches; weight 38 lb. 8 oz.; mentality normal.

The liver was uniformly enlarged 2 inches below the umbilicus at the outer border of the rectus abdominis; it was firm but not hard. The spleen was not palpable. Free fluid was never found in the abdomen.

FAMILY HISTORY. One sibling died and is said to have had a large liver; one other is alive and well.

PATHOLOGICAL INVESTIGATIONS. Age 3 years—

Blood W. R. negative.
Blood W. R. of both parents negative.

Van den Bergh reaction—direct—negative.
indirect—less than 0·5 units.

Faeces—wet film normal.

Age 5 years: Blood count: Red blood cells 4,920,000 per c.mm.; Hb. 80 per cent.; Colour index 0·8; White blood cells 6,800 per c.mm.; polymorphs. 52 per cent.; lymphocytes 46 per cent.; large mononuclears 2 per cent.

Blood sugar curves — Hours
0. 86 mgm. per cent.
1. 160 mgm. per cent.
2. 152 mgm. per cent.
4. 112 mgm. per cent.

Urine—sugar absent and acetone present.

Blood sugar after injecting minims 4 of liq. adrenalin.:

1. 48 mgm. per cent.
2. 50 mgm. per cent.
3. 44 mgm. per cent.
4. 44 mgm. per cent.

Control
1. 69 mgm. per cent.
2. 100 mgm. per cent.
3. 94 mgm. per cent.
4. 89 mgm. per cent.

Urine: sugar and acetone absent.

Age 7 years: Stools contained 14 per cent. starch of dried weight.

Age 8 years: Blood count: Red blood cells 3,060,000 per c.mm.; Hb. 38 per cent.; White blood cells 9,200 per c.mm.

In six weeks the haemoglobin rose to 74 per cent.

Case 2. Male, aged seven years.

HISTORY. Since the age of four years he has had a large abdomen with abdominal pain on hurrying. He eats well, does not vomit and has his bowels open regularly.

PAST HISTORY. Diphtheria, measles and bronchitis. He is said to catch cold easily. He had never been jaundiced.

FAMILY HISTORY. He is an only child.

ON EXAMINATION. Age six years. Weight 41 lb. The liver was $3\frac{3}{4}$ inches below the costal margin at the outer border of the right rectus abdominis; the spleen was not palpable.

Age seven years. Weight 44 lb. The lower border of the liver was at the level of the umbilicus.

PATHOLOGICAL INVESTIGATIONS. Blood count: Red blood cells 4,500,000 per c.mm.; Hb. 86 per cent.; Colour index 0·95; white blood cells 4,000 per c.mm.; polymorphs 49 per cent.; lymphocytes 46 per cent.; eosinophils 3 per cent.; large mononuclears 2 per cent.

Blood W.R. negative.

Van den Bergh reaction: direct and indirect negative.

Blood sugar curve:

0. 120 mgm. per cent. urine—sugar negative, acetone negative.
1. 134 mgm. per cent.
2. 153 mgm. per cent. urine—sugar negative, acetone positive.
3. 157 mgm. per cent.
4. 166 mgm. per cent. urine—sugar negative, acetone positive.

Blood sugar curve after injection of adrenaline 117/111/122/117 mgm. per cent.

Sugar curve after giving test dose of laevulose: 76/92/73/73/73 mgm. per cent.

Galactose tolerance test: 20 gm. of galactose were given by mouth and specimens of urine were collected hourly for five hours. During this period no galactose was excreted in the urine. Normally at least 2 gm. of the sugar should have been excreted.

The dried stool contained 0·7 per cent. of carbohydrate.

Discussion

The two cases described are typical examples of hepatomegalic glycogen disease. They illustrate three points that have received comparatively little attention:

1. The presence of starch in the faeces.
2. The occurrence of the disease in siblings.
3. A past history of jaundice.

STARCH IN THE FAECES. Naish and Gumpert (1935, 1936) described a typical case of glycogen disease in whose stools an enormous quantity of starch was visible microscopically. On analysis the fat content was found to be normal but the dried stool contained 34 per cent. of starch (estimated as glucose). The faeces were three times as potent as those of a normal child in digesting a 1 per cent. starch solution and the diastatic activity remained unchanged after removing all the organisms. The faeces were strongly acid, and after neutralization, fermentation of the starch took place in vitro. These observations appear to have attracted little attention and references to faecal starch are rare in descriptions of cases of this disease. Wagner and Parnas (1921) mention fermentation of the stool in their patient. Van Creveld (1939) found no starch in the faeces of one of his patients. Case 1 had 14 per cent. of starch in the dried stool whereas case 2 had only 0·7 per cent.

FAMILY HISTORY. Although there is no family history of the disease in the majority of cases it is becoming realized that it may occur in siblings.

Such cases have been described by Ellis and Payne (1936) and Bauzá (1935, quoted by Atkinson, 1939) and the cardiomegalic type by Sprague, Bland and White (1931). Probable examples have been reported by Unshelm (1932), Bellingham-Smith and O'Flynn (1933), Lindsay, Ross and Wigglesworth (1935), Krakower (1936) and Antopol et al. (1940); case 1 would come under this heading. Exchaquet (1931) described an interesting family, consisting of a girl aged twelve and twins, a boy and a girl, aged three. All were underdeveloped and had had large livers and ketonuria since birth. The fasting blood sugars were normal but the sugar tolerance curves were abnormal. Sugar tests of liver function were normal but urobilin and urobilinogen were present in the urine and the blood uric acid was raised. The diagnosis of these childrens' illness remains unproved.

PAST HISTORY OF JAUNDICE. A previous history of jaundice has usually been regarded as an independent illness unconnected with glycogen disease but a number of cases similar to case 1 have been reported (Anderson, 1935; Ellis and Payne, 1936; Sundal, 1936; Gardiner and Simpson, 1938; Mason and Anderson, 1941). It seems likely that the jaundice is an integral part of the illness.

Summary

Two typical cases of the hepatic type of glycogen disease are described. In one of them a sibling died with an enlarged liver, there was a past history of jaundice and large quantities of starch were present in the stool.

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